NUMBER 68 MAY 2010

CODE OF PRACTICE REVIEW

PMCPA Prescription Medicines Code of Practice Authority

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the ABPI Code of Practice for the Pharmaceutical Industry independently of the Association itself.

ANNUAL REPORT FOR 2009

The Annual Report of the Prescriptions Medicines Code of Practice Authority for 2009 has now been published and copies will be sent to all who are on the mailing list for the Code of Practice Review. Further copies are available on request.

There were 92 complaints in 2009 compared with 112 complaints in 2008. There were 127 complaints in 2006.

The 92 complaints in 2009 gave rise to 85 cases. The number of cases generally differs from the number of complaints, the reason being that some complaints involve more than one respondent company and some complaints do not become cases at all, because they are not within the scope of the Code or they are withdrawn.

Of the 455 rulings made by the Code of Practice Panel in 2009, 388 (85%) were accepted by the parties, 23 (5%) were unsuccessfully appealed and 44 (10%) were successfully appealed. This compares with the 5% of rulings which were successfully appealed in 2008.

The Code of Practice Panel met 79 times in 2009 (73 in 2008) and the Code of Practice Appeal Board met 9 times in 2009 (9 in 2008). The Appeal Board considered appeals in 15 cases the same as in 2008.

The number of complaints made by health professionals in 2009 exceeded the number made by pharmaceutical companies, there being 40 from health professionals and 24 from pharmaceutical companies. This has historically been the usual pattern although in 1996, 1999, 2001, 2002, and 2003 the reverse was true.

The Authority advertises brief details of all cases where companies were ruled in breach of Clause 2 of the Code, were required to issue a corrective statement or were the subject of a public reprimand. These advertisements act as a sanction and highlight what constitutes a serious breach of the Code.

Three advertisements were placed in the BMJ, The Pharmaceutical Journal and the Nursing Standard in 2009 in relation to complaints received during the year and the remainder were published in 2010.

Copies of the advertisements are on the PMCPA website.

CO-PROMOTION

The supplementary information to Clause 14.1 of the Code states that under co-promotion agreements whereby companies jointly promote the same medicine and the promotional material bears both company names, each company should certify the promotional material involved as they will be held jointly responsible for it under the Code.

Companies are reminded that they will continue to be held jointly responsible for material which bears their name even if a co-promotion agreement has ended. When ending such agreements companies that lose the commercial interest in a product should be very clear as to what will happen to current promotional material particularly if it is to continue to be used by the remaining party and withdrawn some time later. If the material is to be withdrawn some time later, there should be a very clear agreement with the remaining company in that regard – the original co-promotion partners will continue to be jointly responsible for the material which bears their name regardless of which remaining party uses it or withdraws it. Finally, companies are reminded that they must continue to keep certificates and relevant accompanying information for not less than three years after final use of the promotional material (or the date of a meeting) even when the co-promotion agreement has ended.

UPDATED CONSTITUTION AND PROCEDURE FOR THE PRESCRIPTION MEDICINES CODE OF PRACTICE AUTHORITY AGREED

Proposals for amendment of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority were agreed at the Annual General Meeting of the ABPI in April 2010.

The changes to the Constitution and Procedure are available on our website (www.pmcpa.org.uk). They come into operation on 1 January 2011, except for certain provisions which will be operational in respect of complaints and voluntary admissions received on and after 1 January 2011.

PROPOSALS TO AMEND THE CODE

It is hoped that proposals to amend the Code will be circulated shortly for consultation.

CODE OF PRACTICE TRAINING

Training seminars on the Code of Practice, run by the Prescription Medicines Code of Practice Authority and open to all comers, are held on a regular basis in central London.

These seminars comprise a full day course offering lectures on the Code and the procedures under which complaints are considered, discussion of case studies in syndicate groups and the opportunity to put questions to the Code of Practice Authority.

The next Code of Practice seminar date on which places remain available is:
Monday, 18 October 2010

Short training sessions on the Code or full all day seminars can be arranged for individual companies, including advertising and public relations agencies and member and non member companies of the ABPI. Training sessions can be tailored to the requirements of the individual company.

For further information regarding any of the above, please contact Nora Alexander for details (020 7747 1443 or email nalexander@pmcpa.org.uk).

HOW TO CONTACT THE AUTHORITY

Our address is:
Prescription Medicines Code of Practice Authority
12 Whitehall, London SW1A 2DY

www.pmcpa.org.uk

Telephone:	020 7747 8880
Facsimile:	020 7747 8881

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7747 8885 or email lmatthews@pmcpa.org.uk).

Direct lines can be used to contact members of the Authority.

Heather Simmonds:	020 7747 1438
Etta Logan:	020 7747 1405
Jane Landles:	020 7747 1415

The above are available to give informal advice on the application of the Code of Practice.

The Authority rather than the ABPI is the contact point for information on the application of the Code.

MEDIA/DIRECTOR v PFIZER

Celebrex study and meeting

An article in the BMJ, 5 September 2009, criticised a Celebrex (celecoxib) study and meeting. Celebrex was Pfizer's product for the symptomatic relief of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. In accordance with the Authority's Constitution and Procedure, the matter was taken up as a complaint by the Director.

The meeting, at a five star hotel resort in March 2009, had been held to encourage GPs to participate in a major study comparing the cardiovascular safety of Celecoxib vs non-selective non-steroidal anti-inflammatory drugs (NSAIDs). The author of the BMJ article had attended the meeting at the invitation of the study sponsor (a named university).

The BMJ article was critical that the invitation to the meeting did not mention Pfizer although it provided £26 million for the study. The study was described as an 'academic, investigator-initiated study, requested by the European Medicines Agency (EMEA) and sponsored by the (named university)'. The study application form submitted to the NHS research ethics committee indicated that Pfizer was the sole funder of the study.

According to the article, the Saturday morning meeting ended with a three course lunch. Attendees had complimentary drinks and dinner the night before, accommodation at the hotel on the Friday night and their travel reimbursed. The principal investigator stated that attendees received only 'standard set menus and no excessive hospitality was given'. He stressed that GPs had given up a Saturday without pay to be trained in trial methodology.

The article stated that thirty five doctors attended the meeting from 25 practices. Up to four GPs attended from a single practice. Some doctors said their practice had already signed up to the trial. One of them admitted coming along just for the hospitality. Practices that signed up received £1,000 and a further £5 every two months for each patient reporting progress on a web portal. The principal investigator noted that the money went to the practices not direct to the doctors.

The principal investigator defended the study's independence and noted that it was entirely run by the university with no pharmaceutical company involvement in any of its meetings. As such, the Code was inappropriate. A Pfizer spokesman supported the principal investigator's position stating, inter alia, that the study was an investigator driven research project sponsored by the university. Pfizer had financially supported the study, but it was managed and operated independently of the company. The meeting was not organised by Pfizer or on Pfizer's behalf; it was solely the initiative and responsibility of the principal investigator.

The article stated that the trial had been registered on ClinicalTrials.gov which encouraged transparency in clinical research by providing free access to information about funding, sponsorship, methodology, intervention, and research question. There was no mention of Pfizer in the trial registration form. The university had not commented on why it chose to leave out the funding source from the clinical register.

A professor of sociology was reported as being concerned that the study website did not mention Pfizer's funding – a fact also missing from some news pieces announcing the study. 'Neglecting to mention the financial sponsor of the research is deceptive', he stated and 'the recruitment of doctors via entertainment in five star luxury also appears to be ethically questionable'.

The article noted that the study was being conducted so that Pfizer could fulfil a regulatory commitment. COX-2 inhibitors had been monitored since 2004, when rofecoxib was withdrawn because of a risk of thrombotic cardiovascular events and questions were raised regarding the cardiovascular safety of other COX-2 inhibitors. The EMEA had decided to keep celecoxib on the market but to recommend a long term study to investigate its safety relative to non-selective NSAIDs.

The detailed response from Pfizer is given below.

The Panel noted Pfizer's submission and the comments of the principal investigator about their respective roles and responsibilities in relation to the study. The Panel considered that it was important to note the regulatory requirement for the study. Correspondence with the EMEA referred to Pfizer committing to perform a global cardiovascular study to confirm long term safety and to dialogue about the study design with EMEA/CHMP. The Panel noted Pfizer's submission that the principal investigator had acted as a global medical consultant on celecoxib for its parent company, Pfizer Inc, including attending the Oral Explanation before the CHMP. Pfizer explained that a study protocol was drafted by the principal investigator and his academic colleagues, although it was reviewed and amended by Pfizer and EMEA/CHMP. The university was the study sponsor for the purposes of the clinical trial regulations.

The Panel noted that the BMJ article criticised: the level of hospitality provided to potential clinical

investigators and the acceptability of the venue; whether the study was promotional including the acceptability of the level of payments to investigators and whether Pfizer's role in funding the study had been declared.

The first issue to be considered was the extent to which Pfizer was responsible, if at all, under the Code for any of the activities at issue. The Panel noted the regulatory requirement for the study. The Panel noted Pfizer's submission that the trial was an investigator initiated study, run independently of Pfizer; it was carried out at arm's length from Pfizer and without reference to the company.

The Panel noted that the study agreement between Pfizer and the sponsoring university described the parties as independent contractors. The university undertook to keep Pfizer updated on progress at regular intervals and provide quarterly written reports. Monthly teleconferences were also held with Pfizer. Under the study contract Pfizer undertook to provide two representatives to attend as observers to the Executive Committee and Steering Committee. The Panel noted that Pfizer by invitation had attended meetings of the Steering Committee as non voting observers but had rarely been invited to attend any meetings of the Executive Committee.

The Panel noted that Pfizer UK had little involvement in the matters subject to the complaint as its parent company Pfizer Inc led on this matter. The Panel was concerned that the first time Pfizer UK heard about the meeting at issue was when it was contacted by a journalist who wished to attend the meeting which was held in the UK and thus potentially subject to the UK Code. UK health professionals had attended the meeting. It was an established principle under the Code that UK companies were responsible for the acts and omissions of their overseas affiliates that came within the scope of the Code.

Taking all the circumstances into account, the Panel did not accept that Pfizer had absolutely no responsibility under the Code for any aspect of the arrangements. It was not a strictly arm's length arrangement. Pfizer was obliged to initiate the study to satisfy regulatory requirements. On the evidence before the Panel, Pfizer Inc had not included a provision about Code compliance as part of the contract. The Panel noted Pfizer UK's proposal to subsequently amend the contract by adding a relevant provision that the university conduct the study in accordance with 'all applicable laws, regulations and codes of practice'. The Panel noted that on finding out about the meeting Pfizer UK had advised the principal investigator that there was a very high likelihood of Pfizer being associated with it and that it could not allow study funds to be used to hold meetings at a venue such as that proposed. The Panel also noted that, at the university's request, Pfizer had provided it with guidance on how to run an event within the ABPI guidelines. The Panel noted that there might be certain activities which fell solely within the investigator's remit on which the company quite properly had absolutely no influence. However, in the particular circumstances of this case, the Panel considered that it was beholden on Pfizer to use its best endeavours to ensure the contract provided that certain activities such as arrangements for meetings complied with the Code, otherwise the omission of such provisions would be a means of circumventing the relevant Code requirements. This would be unacceptable.

Taking all the circumstances into account the Panel considered that Pfizer UK was responsible under the Code for the matters raised in the article at issue.

The Panel noted that the hotel meeting was designed to educate UK potential trial investigators about the study. The meeting started at 8.30am with registration followed by the first presentation on the study at 9am. The meeting finished at 1pm for lunch. Overnight accommodation and dinner had been provided for 34 doctors, one journalist and 6 study staff. Three GPs, 4 study staff and 1 public relations person attended but did not stay overnight. The overall cost was £215.63 per attendee, including study staff and investigators or £278.01 for delegates. The Panel considered that irrespective of the content, the impression given by holding a half day meeting at the hotel which was a renowned, deluxe venue, including an overnight stay for most delegates, was inappropriate. High standards had not been maintained. The impression given by the arrangements was such that they brought discredit upon and reduced confidence in the pharmaceutical industry. Breaches of the Code were ruled including Clause 2.

A declaration of Pfizer's role in relation to funding the study did not appear on the invitation, agenda or other meeting papers. Pfizer Inc's observer status was referred to on a slide which discussed the organisation of the study but not the company's financial role. A breach of the Code was ruled. The Panel noted that other study material should have clearly indicated Pfizer's role. The Panel noted that the only other relevant piece of material before the Panel was the GP template contract which referred to the Pfizer funding in the first paragraph. The Panel ruled no breach of the Code in relation to the GP template contract.

The only issue to be considered by the Panel in relation to the study was whether it was disguised promotion. In this regard particular reference was made in the article at issue to the run-in period. The study was run independently of Pfizer. Nonetheless the Panel considered that in the particular circumstances of this study it was beholden on Pfizer, before it provided the finance, to satisfy itself that the study was not disguised promotion. The protocol stated that the study was powered to demonstrate that celecoxib was not inferior to standard NSAID therapy in relation to cardiovascular safety. Eligible patients were subject to a 2 week open-label run-in of treatment with

celecoxib. At the end of this period subjects who had taken at least one dose and who did not express a strong preference for either their previous treatment or celecoxib were eligible for randomisation. Appendix 1 to the protocol explained some of the rationale behind the study design and explained that chronic NSAID users who were not taking 'coxib' medicines had demonstrated tolerance to NSAIDs and randomisation without an open phase was thought to introduce a bias in that such subjects would be more likely to tolerate their old medicine than a new one. For this reason the open label phase allowed those who had relatively similar tolerability and efficacy to both therapies prior to randomisation to be included. The Panel noted that the regulators had considered and approved the protocol before recruitment commenced. The Panel did not consider that the points of concern raised in the BMJ article were sufficient to demonstrate that the study was disguised promotion. A reasonable explanation appeared in an appendix to the protocol. No breach was ruled.

The Panel noted that given its ruling of no breach above it thus followed that on the narrow allegation in the article, Pfizer had funded the study for research purposes and the funding to the university did not constitute an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. No breach was thus ruled.

The Panel noted Pfizer's submission about the modest nature of the payments to practices participating in the study. The practice received a one-off payment of £1,000 to search records and contact patients followed by £5 per month for each participant recruited by the practice and £1 per month for the provision of data in relation to each participant. Given its finding of no breach of the Code above, and noting that the level of the payments was not unreasonable, the Panel ruled no breach.

Upon appeal by Pfizer the Appeal Board noted Pfizer's submission and the comments of the principal investigator about their respective roles and responsibilities in relation to the study. The Appeal Board considered that it was important to note the regulatory requirement for the study. The EMEA had reviewed the safety of the COX-2s, including celecoxib (Celebrex) in 2004/5. In June 2005 the CHMP recommended the maintenance of the marketing authorization for Celebrex on the basis that Pfizer initiated a global study to investigate the long term cardiovascular safety of celecoxib relative to non-selective NSAIDs. The Appeal Board noted Pfizer's submission that the principal investigator had acted as an external medical consultant on celecoxib for Pfizer Inc including attending a meeting of the CHMP on Pfizer's behalf and it was in this capacity that he was aware of the CHMP requirement for a study and become involved. Pfizer had initially planned to sponsor the study itself which it submitted was the more usual approach. However, the principal investigator presented a proposed study design which was ultimately accepted by CHMP as suitable in order to meet Pfizer's regulatory commitment. The protocol was reviewed and amended by Pfizer and the CHMP.

The study agreement stated that the university was the study sponsor for the purposes of the clinical trial regulations and Pfizer provided the funding. The university undertook to keep Pfizer updated on progress at regular intervals and provide quarterly written reports. Pfizer Inc personnel were permitted to attend meetings of the Executive Committee and the Steering Committee as non voting observers. Pfizer's attendee's at these meetings had been epidemiologists. After January 2009, monthly teleconferences were also held with Pfizer.

The Appeal Board was concerned that the first time Pfizer UK heard about the meeting at issue was when it was contacted by a journalist who wished to attend the meeting which was held in the UK and thus potentially subject to the UK Code. UK health professionals had attended the meeting.

The Appeal Board noted that once it knew about the meeting in the hotel Pfizer had contacted the principal investigator and requested that the venue be changed as there was a high likelihood of Pfizer being associated with it. However, the university proceeded with the arrangements. Pfizer submitted that it was unable to prevent the meeting taking place and that it had no legal control over the meeting.

The Appeal Board noted from the study agreement that £170,000 was set aside for practice recruitment and initiation meetings for each of the first two years. The Appeal Board was concerned about Pfizer's lack of control or even guidance about how this money was to be used.

The Appeal Board acknowledged that investigator initiated studies made an important contribution to knowledge about medicines and their use. Whether or not they were subject to the Code would depend on the circumstances of each particular case. The fact that some of these studies might be subject to the Code did not, in itself, mean that they could not happen. Each case would be considered on its own particular merits.

The first matter to be decided in this case was whether Pfizer was responsible under the Code for a study it had funded and which was undertaken to satisfy regulatory requirements and maintain Celebrex's marketing authorization. The Appeal Board noted that given the regulatory requirement for the study funded by Pfizer the description used by Pfizer, 'investigator initiated' did not give a wholly accurate impression of the process by which the study was devised.

The Appeal Board noted that when approving protocols etc for company-funded studies regulators imposed certain obligations upon those companies particularly, for instance, with regard to the collection of adverse event data. The mere fact

that a company acted to fulfil its obligation in this regard in what was otherwise a wholly independent study did not necessarily mean that the study could not be considered to be conducted at arm's length. Taking all the circumstances into account the Appeal Board decided that although Pfizer funded the study there was a high degree of independence built into it. The Appeal Board decided that Pfizer was not responsible under the Code for the arrangements of the meeting in question; these were the responsibility of the university. The Code did not apply and thus there could be no breach of it. The appeal was successful.

Notwithstanding its ruling above that the arrangements at the investigator's meeting were not covered by the Code, the Appeal Board was very concerned about the perception of such meetings and their possible adverse effect upon the reputation of the pharmaceutical industry. The Appeal Board was also concerned that the materials circulated for the meeting, including invitations to potential investigators, did not mention Pfizer's funding role. It considered that, in their contracts with study sponsors, companies would be well advised to at least refer to the requirements of the Code in relation to meetings and to transparency in relation to the involvement of the company even if the arrangements, as here, were not subject to the Code.

The BMJ (5 September 2009) featured an article entitled 'In clear sight' which criticised a Celebrex (celecoxib) study and meeting. Celebrex was Pfizer Limited's product indicated for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

The meeting was held at a five star hotel resort in March 2009. The journalist had attended the meeting at the invitation of the university which acted as the sponsor for the study at issue. A similar meeting had been held in January 2009. Both meetings aimed to provide general practices with sufficient information about the study to enable GPs to decide whether to participate.

In accordance with Paragraph 6.1 of the Authority's Constitution and Procedure, the matter was taken up as a complaint by the Director. The author was asked whether she wished to be involved in the case and whether she had any additional information to submit. The journalist did not respond to this request.

COMPLAINT

The article was concerned about the meeting arrangements. The invitation did not mention Pfizer although it provided £26 million for the study. The study was described as an 'academic, investigator-initiated study, requested by the European Medicines Agency (EMEA) and sponsored by the [named university]'. The study application form submitted to the NHS research ethics committee indicated that Pfizer was the sole funder of the study.

The study compared the cardiovascular safety of the cyclo-oxygenase-2 (COX-2) inhibitor celecoxib with that of other non-steroidal anti-inflammatory drugs (NSAIDs) in patients over 60, already taking a non-selective NSAID regularly, and who did not have established cardiovascular or peripheral vascular disease or severe heart failure.

According to the article the journalist was invited to attend the meeting by the principal investigator via a public relations firm that listed Pfizer as one of its clients. The meeting started at 9am on Saturday and ended with a three course lunch. Attendees had complimentary drinks and dinner the night before, accommodation at the five star luxury hotel on the Friday night and their travel reimbursed.

The principal investigator stated that attendees received only 'standard set menus and no excessive hospitality was given'. He also stressed 'GPs had given up their Saturday without pay to be trained in trial methodology'. Further the meeting at the hotel was a cost cutting measure, 'We found that if we rented out a room somewhere during the week, doctors weren't coming. But they are coming if we set up meetings at the weekend at the hotel. This still works out better for us. The whole deal we get from the hotel is a lot less than £300. You could say the recession's helped us do the study'. His argument was that doctors had to be paid a locum fee of £350 a day if the meetings were held during the week and one partner had to leave the surgery.

The article stated that thirty five doctors attended the meeting from 25 practices. Up to four GPs attended from one practice. Some doctors said their practice had already signed up to the trial. One of them admitted coming along just for the hospitality. Another joked, 'If we don't sign up now, does that mean we get to come to [the hotel] again and again until we make our minds up?'.

Practices that signed up received £1,000 and a further £5 every two months for each patient reporting progress on a web portal. The principal investigator stated: 'Some practices have more than 50 patients. That's quite a lot of money, but it goes to the practice. The university does not sign any cheques for doctors'.

The principal investigator defended the study's independence and submitted that the trial created vital research capacity. It was entirely run by the sponsoring university with no pharmaceutical company involvement in any of its meetings. As such, mention of the Code was inappropriate. The article referred to the requirements of Clause 19.1 of the Code and advice that companies were asked 'would you and your company be willing to have these arrangements generally known?' when determining whether the arrangements for any meeting were acceptable.

A Pfizer spokesman supported the principal investigator's position that the ABPI Code did not

apply. The study was an investigator driven research project led by the principal investigator of the university which sponsored the study. Pfizer had financially supported the study, but it was managed and operated independently of Pfizer. This meeting was not organised by Pfizer or on Pfizer's behalf; it was solely the initiative and responsibility of the principal investigator and the sponsoring university.

The article quoted a doctor commenting that '…this is obviously not how patients for trials should be recruited. Doctors should be encouraged to recruit in a trial because they think it's a good thing and will be beneficial for the patient. There are loads of ways they could go about recruiting for trials – they could go to health centres, have lunch meetings, for example – the hotel would seem inappropriate to most people. I would also question whether the overnight stay is necessary. Most doctors could have driven to the meeting in the morning'.

A senior lecturer in clinical pharmacology, also had reservations: 'Like all academic research projects with external funding, Pfizer has agreed to provide a certain sum of money to pay for the trial, and this will include costs of recruitment and investigators' meetings – in the hotel for this particular study. The money has been given to the university, but the source is still commercial'.

The lecturer referred to a meeting he had held for 12 researchers which cost roughly £300 – sandwiches in a small hotel right next to a railway station. There were lavish meetings and frugal – usually tax payer funded – ones, he stated 'the principal investigator was only able to hold the meeting in question at the hotel because money was coming from Pfizer. There would be no chance of the university agreeing to pay for such a meeting from university funds'.

The lecturer, who specialised in developing methods for evaluating data on adverse effects, was also concerned about the design. Patients all underwent a run-in phase before randomisation where they took celecoxib for two weeks before being allowed to take full part in the trial. The lecturer questioned the effect of this run-in phase. In his opinion, all those who suffered side effects from celecoxib would drop out in the first two weeks, thus ensuring that only those who did well with celecoxib continued. He had strong concerns about the study design as the safety data would not be as valid as with other designs.

A professor of biostatistics and biomathematics, who specialised in clinical trials design and analysis, agreed stating that the run-in would remove patients with unfavourable cardiovascular or gastrointestinal response. Those with side effects to celecoxib would be out of the study. Using a run-in with so many completed studies on celecoxib was silly. The study should be revised and the run-in deleted.

A spokesman for Pfizer noted that: 'the study was an investigator driven research project and stated that the study sponsors should be contacted for a response to questions relating to the conduct of the study.

The sponsoring university declined to comment on the specific criticisms of the trial design but had released the full protocol after a request under the Freedom of Information Act. The document provided a rationale behind choices of study design: 'The trial identifies chronic NSAID users in the population who were not taking 'coxib' [COX-2] drugs. These subjects have demonstrated tolerance to NSAIDs. Switching of drug therapy to celecoxib as would happen to 50% of subjects if randomization occurred without an open label phase was thought to introduce a bias in that subjects would be more likely to tolerate their previous drug than the new one. For this reason the open label phase allows those who have relatively similar tolerability and efficacy to both therapies prior to randomization'.

The document explained that at the end of the run-in period, 'Subjects who have taken at least one dose of celecoxib and who do not express a strong preference for either their previous treatment or celecoxib will be eligible for randomization. Preference will be determined by the patient response to a questionnaire'.

The article stated that the trial had been registered on ClinicalTrials.gov which encouraged transparency in clinical research by providing free access to information about funding, sponsorship, methodology, intervention, and research question. Its policy was consistent with US law and did not require the listing of collaboration or funders if they were not considered the sponsor. There was no mention of Pfizer in the trial registration form.

A spokesperson for the International Committee of Medical Journal Editors (ICMJE) stated: 'As stated in the ICMJE policy, funding source or sponsor is a required field for registration. Without this information, the ICMJE would consider registration insufficient'.

A spokesperson for Pfizer stated: 'Pfizer considers investigator driven research to be important in advancing disease treatments and consequently improving the lives of patients. Pfizer encourages all investigators to disclose information on research they are conducting; however, there is no formal requirement for them to do so'.

The university had not commented on why it chose to leave out the funding source from the clinical register.

A professor of sociology, also raised concerns that the study website did not mention funding from Pfizer – a fact also missing from some news pieces announcing the study. 'Neglecting to mention the financial sponsor of the research is deceptive', he stated 'On the other hand the recruitment of doctors via entertainment in five star luxury also appears to be ethically questionable'.

The director of a university institute of medical

humanities who specialised in ethical issues in primary care and professional integrity in clinical research added: 'The purpose of the study in the trial register reads more like a press release promoting celecoxib than a statement of today's science. The notion that other NSAIDs pose a significant cardiovascular risk, comparable to that of COX-2 drugs, is a very dubious claim. This certainly makes me worried that the information to be presented to research subjects will sound more like a marketing ploy and less like an assessment of the science'.

The participant information sheet presented to potential research subjects stated that 'One NSAID which appears to be at least as safe as most NSAIDs and may be safer than some is celecoxib'. The document highlighted that 'there have also been a number of recent studies of this group of drugs [COX-2s] some of which have suggested there may be a link between these newer drugs and increased heart disease and strokes. For Celebrex [celecoxib], this evidence is not conclusive and there have been many studies that have shown no increased risk of heart disease and strokes'. It pointed to a recent meta-analysis suggesting that cardiovascular effects for celecoxib were similar to those of other NSAIDs and stated 'there is also evidence that older NSAIDs have cardiovascular effects'.

The article stated that the principal investigator insisted that 'This isn't a commercially viable trial for Pfizer. It's not going to help their business model. They're doing this because they have to fill a regulatory EMEA commitment'.

The health regulator had monitored COX-2 inhibitors since 2004, when rofecoxib was withdrawn because of a risk of thrombotic cardiovascular events and questions were raised regarding the cardiovascular safety of other COX-2 inhibitors. As part of the EMEA's December 2005 decision to keep celecoxib on the market, it recommended a long term study to investigate its safety relative to non-selective NSAIDs. An EMEA spokesperson stated: 'You cannot force anyone to conduct clinical trials, but if a company wants its product to stay on the market then we need to be convinced that it should be there. It is in Pfizer's commercial interest to do it'.

When writing to Pfizer the Authority asked it to respond in relation to Clauses 2, 9.1, 9.10, 12.2, 18.1, 18.6, 19.1 and 19.3 of the Code.

RESPONSE

Pfizer explained that as a result of the withdrawal of another COX-2 inhibitor, rofecoxib, in September 2004 due to safety concerns, the European Commission recommended that the cardiovascular safety of all COX-2 inhibitors should be re-examined. The CHMP subsequently required a commitment by Pfizer to undertake a global study to confirm the long term cardiovascular safety of celecoxib. Pfizer also agreed to discuss the design of such a study with EMEA/CHMP.

The study initially designed by Pfizer Inc and approved by the FDA was not acceptable to CHMP as in its view it did not reflect actual use of Celebrex in Europe. The principal investigator, a university professor, was one of Pfizer's external experts during this procedure and, when it became clear that the initial study design could not be modified to meet the CHMP's requirements, he proposed an alternative design, which was ultimately accepted by CHMP and became the study at issue. This study would be conducted in the EU, while the initial study design would be conducted in non-EU countries including the US.

The protocol was drafted by the principal investigator and his academic colleagues and, although it was reviewed and amended by Pfizer and by EMEA/CHMP, most of the study documentation was prepared by the principal investigator and his team and the study design remained essentially as those academics had envisaged. The final study protocol was agreed in July 2007. The study contract between Pfizer Inc and the sponsoring university, under which Pfizer Inc funded the study, was entered into in July 2007 and the study commenced in 2008. Pfizer's funding of the study was made clear in section 14.5 of the study protocol and the participant information sheet, which informed prospective study participants that 'Pfizer, the company who have developed celecoxib, is giving a grant to the [named university] to allow this study to be done'.

The study, a large streamlined safety study (with a prospective randomised open blinded end-point design) was developed to compare the cardiovascular safety of celecoxib with that of traditional NSAIDs. Inclusion criteria were patients sixty years of age or older with clinically diagnosed osteoarthritis or rheumatoid arthritis who were free from established cardiovascular disease and who required chronic NSAID therapy. Patients who signed informed consent and met inclusion and exclusion criteria were then entered into a two-week (14 +/- 7 days) open-label run-in of treatment with celecoxib. (The primary objective of the open-label run-in was to include subjects with relatively similar tolerability and efficacy to both therapies prior to randomisation). At the end of the run-in, patients who had taken at least one dose of celecoxib and who did not strongly prefer either their previous treatment or celecoxib were eligible for randomisation. Medication was taken by the patient consistent with clinical practice on an as required basis. At the time of the protocol completion, it was anticipated that participants would be followed up for an average of 2 years. The primary endpoint of the study was the first occurrence of hospitalisation or death for the Anti-Platelet Trialists' Collaboration (APTC) cardiovascular endpoint of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death.

The study was designed to reflect real life use of medicines, and was a type of study that the principal investigator had advocated for many years. As

stated by a participating GP, in a 'rapid response' to the BMJ article, '[This] is an academic study, run to the protocol developed by [named professors] and managed jointly with other academics from [other universities]'. Two of the named professors, in response to the article stated that it was incorrect to describe the study as 'a Pfizer study' and further explained that: 'The European Medicines Agency (EMEA) obliged Pfizer to fund such a trial if it was feasibly [sic] to do so'. We responded by designing a study that EMEA regarded as feasible and required Pfizer to fund. The study was welcomed by the Chief Medical Officer, Chief Pharmacist and Chief Scientist in [a named country] in part because it tried to develop methodology to extend the ability to do outcomes studies to non-industry investigators …'.

Whilst Pfizer Inc funded the study, the study design was essentially the work of the principal investigator and his academic colleagues, and he was concerned that the study should be run independently of Pfizer and that the university would act as sponsor for the purposes of the clinical trial regulations.

The study protocol provided that the study would be overseen by an Executive Committee. According to the contract, two representatives of Pfizer could be present at meetings of the Executive Committee as observers, although they were not permitted to vote. In addition a Steering Committee would be established to oversee the conduct of the study. Pfizer had no contractual right to participate in or observe the Steering Committee, but had in practice been invited to attend all Steering Committee meetings in non-voting capacity. [A second university] supervised monitoring of the study and also undertook quality assurance, reporting its findings to the sponsoring university. Similarly, [a third university] would be responsible for the statistical analysis of the study data, similarly under contract to the sponsoring university. An independent data monitoring committee was also planned to be constituted to review unblinded data and recommend any necessary study modifications, to the Steering Committee.

The running of the study was therefore determined and conducted entirely independently of Pfizer, save for the fact that Pfizer representatives could contractually be present as observers at meetings of the Executive Committee and had attended meetings of the Steering Committee as non-voting members. In practice, however, Pfizer had rarely been invited to any meetings of the Executive Committee and had not been party to any decisions made by it.

As of January 2009, the team of relevant personnel based at Pfizer Inc in the US met by teleconference with the study sponsor's team, on a weekly and subsequently bi-weekly basis. The aim of these study team meetings was to share information on the progress of the study, particularly in relation to enrolment and, in view of Pfizer's regulatory commitment to the EMEA, for Pfizer to share with the sponsor's team, its skills or expertise relevant to improving enrolment of both GPs and patients.

Meeting at the hotel

Both Pfizer Inc and the sponsoring university recognised that the principal investigator needed to hold meetings with GPs to tell them about the study so that they could consider whether to take part. £170,000 per year for years 1 and 2 was allocated for the purposes of practice recruitment and initiation meetings with a further £10,000 in year 3. The recruitment strategy was not specified in the contract or the study protocol and the arrangements were matters to be determined by the principal investigator as he considered appropriate in all the circumstances, together with all the other arrangements for the study. The study payment schedule was provided.

On 28 January 2009, at meeting of the study team, reference was made to a recruitment meeting to be held on 30/31 January for GP practices which were not yet participating in the study. The meeting was informed that 40 GPs would attend this recruitment meeting to learn about the study and consider taking part. According to the minutes of the meeting and the recollection of the Pfizer team, no information was provided about the location for the meeting or the arrangements.

At the next meeting of the study team, 4 February 2009, Pfizer Inc personnel requested feedback from the recruitment meeting on 30/31 January and were told, for the first time, that the meeting had been held at the five star hotel in question. In the circumstances of this investigator led study, the Pfizer Inc US personnel did not view the choice of hotel as a cause for concern.

On 24 March Pfizer UK received an enquiry from a freelance journalist about the 30/31 January meeting. This was the first time the UK organisation knew that a meeting related to the study had been held at the hotel, and the US team was alerted to the UK perspective on the use of such venues, in the context of the principles of the Code, albeit that this was an event organised and controlled by the study sponsor, independently of Pfizer. Pfizer's response to the journalist's questions were shared with the principal investigator in advance. He agreed with the responses; in his view he was fully responsible for the meeting and would defend his choice of venue publicly.

On 25 March 2009, at a further meeting of the study team, Pfizer Inc discovered that another meeting had been arranged at the hotel on 27/28 March and that 34 GPs were expected to attend. Pfizer Inc personnel expressed concern about the venue in the context of the principles of the Code. The principal investigator explained that the meeting was educational and wholly independent of Pfizer and therefore unobjectionable. He maintained that the hotel was more cost-effective than other venues as a result of the favourable terms negotiated and the fact that, because the meeting would be on a Saturday, the cost of locum cover for attending GPs was avoided. Finally he advised the study team that he had invited

the freelance reporter who had previously contacted Pfizer, to attend the meeting, so that she could see for herself that the meeting was educational and that there was nothing untoward about the arrangements.

After the study team meeting, Pfizer discussed internally the proposed meeting at the hotel and the principal investigator's comments. While the study was investigator designed and driven and the meeting arrangements were wholly the responsibility of the investigator, Pfizer was concerned that, as Pfizer Inc had funded the study, Pfizer would be linked with the meeting and that such association might be viewed as inconsistent with the principles of the Code. Pfizer was unable to compel the principal investigator to rearrange the meeting, in accordance with the contractual arrangements between Pfizer and the university, or otherwise. Accordingly, after several unsuccessful attempts to telephone him, Pfizer emailed him, in the strongest terms, to ask him to change the arrangements for the meeting, in particular to ensure that it was held at an alternative venue to mirror the principles of the Code, in order to guard against potential reputational damage to Pfizer or the university. A copy of the email was provided. Nonetheless the meeting proceeded as originally planned and Pfizer received no reply to the concerns expressed in its email or to its request that the meeting be rearranged at a different venue.

The meeting at the hotel was discussed at the next meeting of the study team on 1 April 2009. The principal investigator reported that he had contacted the PMCPA and had established that the sponsor university was not subject to the Code. It was unclear whether he had contacted the PMCPA before or after the meeting and what information he had provided during that discussion. He commented that it was difficult to find any other appropriate meeting venue nationally and reiterated his view that the hotel was cost-effective and appropriate. He strongly objected to Pfizer's email.

However, at the end of April, the university's team asked Pfizer to suggest appropriate alternative venues for the meetings in question. On May 7 Pfizer sent to the sponsor an article entitled '10 Ways to Run an Event Within the ABPI Guidelines', a practical guide. To Pfizer's knowledge, since the March recruitment meeting, no further meetings had been held at the hotel at issue or any similar venue that might be viewed as inconsistent with the principles of the Code.

While the study was investigator initiated, and Pfizer had no wish to prejudice the independence of the investigator/sponsor in its organisation or arrangements, the company was concerned that the meeting at the hotel could result in adverse reputational consequences for Pfizer and for the university principal investigator. Therefore, when on 8 June 2009 Pfizer sent a proposed contract amendment to the university, this included, inter alia, an amendment seeking to strengthen the existing wording in the contract on the governance of the study such that Pfizer would require the university to conduct the study in accordance with 'all applicable laws, regulations, and codes of practice', in an attempt to reinforce the points made to the university in March concerning the principles of the Code. The university had not formally responded to this amendment request.

In summary, Pfizer had no involvement whatsoever in either of the two meetings held at the hotel in January and March 2009. Pfizer only knew about the January meeting after it had taken place and about the March meeting two days beforehand. Pfizer was not involved in the initiation or running of the meetings and no-one from Pfizer attended either meeting. The meeting materials prepared by the principal investigator and his team were not discussed with or shown to Pfizer. While it seemed likely that Pfizer Inc's funding for practice recruitment and initiation meetings during the study would have paid for the meetings in question, such expenditure was not discussed with, specifically invoiced to or approved by Pfizer, and Pfizer did not know how much was spent on the meetings. As it was not present at or involved in the meetings, Pfizer had no first hand knowledge of these matters, however some further information had been published by the doctors who submitted rapid responses to the article published in the online version of the BMJ (see below).

The principal investigator advised Pfizer Inc that 40 GPs attended the meeting in January 2009 and that 34 were due to attend the meeting in March. The BMJ article stated that 35 GPs attended the meeting on 27/28 March. Pfizer could not confirm the accuracy of these figures. Pfizer had not seen any of the material used by the principal investigator during the meetings at the hotel. No agency was involved on behalf of the company in relation to such meetings. As Pfizer had had either no advance knowledge (January) or minimal advance knowledge (March) of the meeting there was no opportunity for the company to ensure that materials used had included a declaration that funding had been provided by Pfizer.

Pfizer had no specific knowledge of the role of the public relations agency in respect of the study or the meetings at the hotel. Pfizer assumed that the university had hired the agency to assist with the meeting arrangements and/or communications. The BMJ article stated that the public relations agency claimed that Pfizer was a client - however any relationship between Pfizer and the agency was unrelated to the study.

Immediately following the publication of the article in the BMJ, a rapid response letter from a GP and trial physician, involved with running the study at the sponsor university, was published on the BMJ website. A copy of this response was provided.

- The GP justified the use of the hotel to recruit doctors and indicated that other presentations

had been given at smaller locations. He confirmed that 'there was no golf, spa treatments or any other luxurious indulgence going on' during the meeting. He concluded 'in exchange for giving up this Saturday morning to hear about and decide whether to take part in one the largest academic NSAID safety studies ever attempted, GPs were provided with free dinner, B&B and/or lunch. Concerning the venue they expressed a preference for a hotel without sticky carpets'.

- The GP also stated that Pfizer's funding had never been secret. He said 'it is irrelevant because [the study] is an academic study run to the protocol developed by [named professors] and managed jointly also with other academics.

- He confirmed his view that the money offered to practices to take part in the study was appropriate and 'money has not been an incentive as most practices have fewer than 20 eligible patients and the sums involved are nominal'.

- Finally, he justified the design of the study stating 'patients who do a lot better, as well as those who do worse, on celecoxib compared with their usual NSAID are both excluded from randomisation. This is because we need to observe patients for a considerable time to detect differences between all NSAIDs in their cardiovascular risk effects and during that time they need to stay on their randomised therapy. Therefore we select patients who don't care if they are randomised to celecoxib or their old NSAID. That is not what you do if you are trying to bias the results in favour of celecoxib'.

A second rapid response letter, from the two professors who were co-authors of the study protocol, was subsequently published on the BMJ website. A copy of this letter was provided.

- The two professors corrected the characterisation of the study as 'a Pfizer study', explaining its academic origins and design and Pfizer's obligation to fund it, in light of the company's obligation to the EMEA.
- They explained the necessity of the 'run-in period' and denied that the purpose of the study was marketing-related.
- With regard to the meeting venue, they suggested that the cost was likely to be no more and possibly less than other less famous venues and stated that the Comprehensive Research Networks established by the UK government encouraged 'similarly-costed away days to increase awareness and interest and which pay trial participants comparable amounts for their activity'. Finally they underlined the importance and challenge of encouraging individuals to take on research responsibilities 'in a target-driven clinical world'.

Responses to the clauses from the Code

The BMJ article referred only to the hotel meeting in March 2009 attended by the journalist. Nevertheless in circumstances where, as explained above, Pfizer understood that two meetings were held, it addressed both of these in its response.

Clauses 9.1 and 9.10

Clause 9.1 of the Code provided that high standards must be maintained at all times and Clause 9.10 stated that material relating to medicines and their uses, sponsored by a pharmaceutical company must clearly indicate that it had been sponsored by that company. In this context, the BMJ article stated that the invitation to the March meeting did not mention the provision of funding by Pfizer.

As indicated above, the trial was an investigator initiated study, run independently of Pfizer. The organisation of the study was carried out at arm's-length from Pfizer and without reference to the company. While Pfizer funded the study, a requirement that it be responsible for every action by the investigator and every document generated by the investigator would be inconsistent with fact that the study was an investigator initiated study and with the status and responsibilities of the investigator in this case, as sponsor in accordance with the clinical trial regulations. Furthermore, it was not clear from the wording of the Code that Clause 9 was directed towards material generated by an investigator in an investigator initiated study or that, in the circumstances of the study at issue, Pfizer was obliged to supervise all arrangements by the sponsor or to certify all materials generated by the sponsor in connection with the study.

In the context of the BMJ article Pfizer did not know about the January meeting at the hotel until after it had been held and received two days' notice of the meeting in March. Pfizer was not invited to the meeting nor provided with the agenda or any of the materials prepared by the sponsoring university for the meetings either before they took place or afterwards. It therefore had no knowledge of the materials used by the principal investigator or whether they referred to Pfizer's funding of the study. The contractual arrangements between Pfizer and the sponsoring university did not require the university to disclose such materials to Pfizer or to agree them with the company, as was appropriate given the university's position as study sponsor, being solely responsible for the conduct and operation of the study.

In relation to the assertion that announcements and press statements had not referred to Pfizer funding, to the extent that any had been made by Pfizer (such as the comments given to the journalist), Pfizer had always made this clear. Pfizer had not been consulted on or involved in announcements made by the university, but noted that one recent article concerning the study, published in the lay press on 19 August and extensively quoting the principal investigator, referred to the study being funded by Pfizer.

Clause 12.2 – Disguised promotion

The study at issue was an investigator initiated study set up at the request of the EMEA/CHMP. The study was designed by the principal investigator and his academic colleagues, and while the original draft protocol was amended following input from both Pfizer and the EMEA/CHMP, the final protocol was essentially his work. The protocol was considered in detail with the EMEA/CHMP and approved by them before recruitment commenced.

Pfizer funded the study in order to satisfy a regulatory obligation imposed by the EMEA/CHMP. The company vigorously refuted any suggestion that the study was disguised promotion.

Clauses 18.1 and 18.6 - Gifts, inducements, promotional aids and the provision of medical and educational goods and services

The BMJ article referred to the fact that practices that agreed to take part in the study would receive £1,000 and a further £5 every two months for each patient reporting progress on a web portal. As was appropriate in an investigator driven study of which the university was the sponsor, Pfizer had not been involved in determining these sums or making these arrangements. However, Clause 8 the GP template contract supplied by the university to Pfizer (solely for information) in January 2009 read: 'The Practice shall receive the sum of £5.00 per month for each Study Participant recruited to the Study by the Practice, plus £1.00 per month per Study Participant for the provision of prescribing data in relation to each Study Participant which sums will be paid by the University quarterly in arrears based on the Study data records held by the University detailing recruitment/retention at the Practice. In addition a one off payment of £1000.00 shall be paid to the Practice in relation to searching records and writing to patients required in relation to the Study'.

Although not involved in determining these figures, Pfizer considered that they represented a fair payment for the time spent by a GP in considering the study materials and identifying patients who appeared to be potential study subjects as well as providing the required follow-up information. Certainly they seemed well below the level customarily paid in industry sponsored clinical trials. In this regard, according to the relevant section of the British Medical Association website which set out suggested payment rates for various types of work for pharmaceutical companies, the rate suggested for clinical trial work was £223 per hour. £1,000 payment therefore represented a little over four hours' work at this rate, which seemed entirely reasonable for the work required. These payments thus did not incentivise doctors to take part in the study.

With respect to Clause 18.6, as indicated in the response to Clause 12.2 above, the study was a genuine scientific study, designed with substantial input from the EMEA/CHMP and approved by them. The study was not organised or run by Pfizer: Pfizer had funded the study in order to satisfy a regulatory obligation. The study constituted genuine research and not an inducement to prescribe, supply, administer, recommend, buy or sell any medicine.

Clauses 19.1 and 19.3 - Meetings and hospitality

The BMJ article criticised the meeting at the hotel in relation to the level of hospitality provided (explicit reference to Clause 19.1 was included in the article) and because the invitation did not state that funding had been made available by Pfizer.

The principal investigator's position was that he arranged for the hotel meetings independently of Pfizer and that they were not objectionable. The principal investigator was not subject to the Code and had confirmed the position with the PMCPA. He believed that the hotel represented a cost-effective use of resources and that GPs who were willing to give up a Saturday morning in order to learn about the trial, in reasonably comfortable surroundings. Finally, Pfizer knew of no evidence that any of the GPs who attended the meeting used any of the hotel's sporting facilities. The journalist was invited to the meeting by the principal investigator without reference to Pfizer.

As Pfizer had explained, it was not involved in the arrangements for either meeting held at the hotel, as was appropriate given that the university was the sponsor and entirely responsible for its conduct and operational arrangements. While the principal investigator maintained strenuously that the Code was not applicable to meetings organised by the sponsoring university, Pfizer was nevertheless concerned that it would be linked with the meeting. Pfizer therefore strongly requested the principal investigator to change the venue, but the university proceeded with the arrangements and Pfizer was unable to prevent the meeting taking place. While Pfizer's funding was intended to include support for meetings for the study it would have been inappropriate for Pfizer to request involvement in the operational arrangements. In any event, from the description of the meeting provided by a GP in his response to the article, the actual meeting arrangements and hospitality were not lavish.

As indicated above, the BMJ article stated that the invitation to the meeting did not state that the study was sponsored by Pfizer. Pfizer had explained that it had had no prior knowledge of the meeting and was not provided with the agenda or any of the meeting materials. The company was thus unable to confirm the accuracy of the BMJ article in this regard.

Clause 2 - Discredit to, and reduction of confidence in, the industry

While Pfizer would have preferred the meeting to have been held at a different venue, thereby avoiding any controversy, it believed that a finding of a breach of Clause 2, in the circumstances, would be unfair and disproportionate. The study was a

genuine, major scientific study, established at the request of the EMEA/CHMP, designed and run by the principal investigator and his academic colleagues, and approved by EMEA/CHMP following detailed consideration of the study protocol. As explained above, the sponsor of the study was a university.

As such, the meeting at the hotel was organised and held without Pfizer's input or its knowledge as was appropriate in the circumstances where, as study sponsor, the university was entirely responsible for the conduct of the study and its operational arrangements. Nevertheless, as soon as it knew about the matter the company strenuously tried to persuade the principal investigator to hold the March meeting elsewhere, in order to guard against any reputational damage to Pfizer (and therefore the wider pharmaceutical industry), or the university itself. Despite its efforts Pfizer was unable to prevent the meeting taking place. There were no other measures which Pfizer could reasonably have taken in order to change these meeting arrangements.

While it could not confirm the content of the materials distributed at the hotel meetings, in circumstances where Pfizer had no knowledge of the meetings and was given no opportunity to review the documents, it was unable to require that a statement regarding Pfizer funding of the study was included.

The circumstances described did not warrant the level of censure that should be reserved for a breach of Clause 2.

Further Information

In response to a request for further information Pfizer provided additional comment and documentation.

Pfizer noted that it had not previously asked the sponsoring university for the detailed information requested by the Authority about the meeting on 27/28 March 2009, believing it inappropriate in the context of an investigator run study where the university as sponsor was solely responsible for such organisational matters, and given that the university had no obligation to disclose such information to Pfizer under the study contract. However, following the Authority's request for further information Pfizer requested this information from the principal investigator. The principal investigator declined to provide this information directly to Pfizer but had offered to provide it directly to the Authority. Pfizer did not object to him doing so, and was aware that the Authority had now informed him that he must either copy Pfizer so that it received the same information, or send it directly to Pfizer as originally requested. Pfizer had no preference as to either route.

The study was a matter of international importance for all of the companies in the Pfizer group, The global medical and clinical teams for Celebrex, based in the US, drove the arrangements for the study and were the contact points with the sponsoring university for the purposes of the study. All relevant affiliates of Pfizer, including Pfizer Limited, as marketing authorization holders for Celebrex in the EU (and elsewhere), knew about the CHMP opinion and the commitment to the EMEA, and the design, objectives and progress of the study. European regional medical colleagues for Celebrex based in the UK would have been similarly well informed about the medical aspects of the study. European regulatory and European legal colleagues based in the UK were closely involved in the regulatory procedures and regulatory/legal aspects. However the Pfizer UK organisation was not involved in the operational, regulatory or contractual arrangements for the study. No advice was requested from the Pfizer UK organisation in this regard. Pfizer Limited UK first knew about the study meeting at the hotel on 24 March, when it received the enquiry from the journalist. It was then that the UK organisation advised the global team with respect to this matter.

Further material was received from the principal investigator including details of the meeting costs and a copy of the presentations. Pfizer confirmed on 26 November that the principal investigator's submission could be treated as part of its response.

The principal investigator accepted the PMCPA's role as a regulator of the marketing practices of pharmaceutical companies, but could not understand why a research meeting organised and run by a university, which was the legal sponsor of the trial protocol written and owned by university investigators, could be construed as within the PMCPA's remit. The investigators had agreed to provide the data requested but only because Pfizer asked them to do this.

PANEL RULING

The Panel noted Pfizer's submission and the comments of the principal investigator about their respective roles and responsibilities in relation to the study. The Panel considered that it was important to note the regulatory requirement for the study. The position was set out in the CHMP opinion dated 23 June 2005 which recommended the maintenance of the marketing authorization and, inter alia, also recommended that Pfizer initiated a long term study to investigate the safety of celecoxib relative to non-selective NSAIDs. Subsequent correspondence with the EMEA referred to Pfizer committing to perform a global cardiovascular (CV) study to confirm long term CV safety and to Pfizer's commitment to dialogue about the study design with EMEA/CHMP. The Panel noted that the BMJ article commented on the role of the principal investigator. The Panel noted Pfizer's submission that he acted as a global medical consultant on celecoxib for its parent company, Pfizer Inc, including attending the Oral Explanation before the CHMP. Pfizer explained that a protocol was drafted by the principal investigator and his academic colleagues, although it was reviewed and amended

by Pfizer and EMEA/CHMP. The university was the study sponsor for the purposes of the clinical trial regulations.

The Panel noted that the BMJ article criticised three key matters: the level of hospitality provided to potential clinical investigators and the acceptability of the venue; whether the SCOT study was promotional including the acceptability of the level of payments to investigators; and whether Pfizer's role in funding the study had been declared.

The Panel noted in relation to the study itself the relevant provision in the Code was Clause 12.2 which required that clinical assessments, post-authorization studies and the like must not be disguised promotion and must be conducted with a primarily scientific or educational purpose. In addition the supplementary information to Clause 19, Meetings and Hospitality, made it clear that, inter alia, investigator meetings for clinical trials were covered by the Code.

The first issue to be considered was the extent to which Pfizer was responsible, if at all, under the Code for any of the activities at issue. The Panel noted the regulatory requirement for the study. The Panel noted Pfizer's submission that 'The trial was an interventional, investigator initiated study, run independently of Pfizer. The organisation of the study was carried out at arm's-length from Pfizer and without reference to the company'.

The Panel considered that, in general terms, the extent to which a company was responsible for study arrangements had to be decided on a case by case basis on the individual facts of each case. The Panel noted that the arrangements between Pfizer and the university at which the principal investigator was based were set out in the study agreement to which the study protocol was annexed. The agreement described the parties as independent contractors. The university undertook to keep Pfizer updated on progress at regular intervals and to provide quarterly written reports on the study progress in terms of enrolment, study centre rollout and other material issues arising in relation to the study. Monthly teleconferences were also held with Pfizer. Under the study contract Pfizer undertook to provide two representatives to attend as obververs to the Executive Committee and Steering Committee. The Panel noted that Pfizer, by invitation, had attended meetings of the Steering Committee as non voting observers but had rarely been invited to attend any meetings of the Executive Committee.

The Panel noted that the position was complicated as Pfizer UK had little involvement in the matters subject to the complaint as its parent company Pfizer Inc led on this matter. The Panel was concerned that the first time Pfizer UK heard about the meeting at issue was when it was contacted by a journalist who wished to attend the meeting which was held in the UK and thus potentially subject to the UK Code (as set out in the supplementary information to Clause 1.7). UK health professionals had attended the meeting. It was an established principle under the Code that UK companies were responsible for the acts and omissions of their overseas affiliates that came within the scope of the Code.

Taking all the circumstances into account, the Panel did not accept that Pfizer had absolutely no responsibility under the Code for any aspect of the arrangements. It was not a strictly arm's length arrangement. Pfizer was obliged to initiate a long term study to investigate the safety of celecoxib vs non-selective NSAIDs to satisfy regulatory requirements and chose to do so via the study. On the evidence before the Panel, Pfizer Inc had not included a provision about Code compliance as part of the contract. The Panel noted Pfizer UK's proposal to subsequently amend the contract by adding a relevant provision that the university conduct the study in accordance with 'all applicable laws, regulations and codes of practice'. The Panel noted that on finding out about the meeting Pfizer UK had advised the principal investigator that there was a very high likelihood of Pfizer being associated with it and that it could not allow study funds to be used to hold meetings at a venue such as that proposed. The Panel also noted that, at the university's request, Pfizer had provided it with guidance on how to run an event within the ABPI guidelines. The Panel noted that there might be certain activities which fell solely within the investigator's remit on which the company quite properly had absolutely no influence. However, in the particular circumstances of this case, the Panel considered that it was beholden on Pfizer to use its best endeavours to ensure the contract provided that certain activities such as arrangements for meetings complied with the Code, otherwise the omission of such provisions would be a means of circumventing the relevant Code requirements. This would be unacceptable.

Taking all the circumstances into account the Panel considered that Pfizer UK was responsible under the Code for the matters raised in the article at issue.

The Panel noted that the supplementary information to Clause 19.1 stated, inter alia, that a meeting venue must be appropriate and conducive to the main purpose of the meeting; lavish, extravagant or deluxe venues must not be used. Venues renowned for their entertainment should be avoided. It should be the programme that attracted delegates and not the associated hospitality or venue. The impression created by the arrangements must be borne in mind.

The Panel noted that the meeting was designed to educate UK potential trial investigators about the study. The meeting started at 8.30am with registration followed by the first presentation on the study at 9am. This was followed by presentations on the role of nurses, data collection for research nurses, and monitoring and good clinical practice (GCP) training finishing at 1pm for lunch. Overnight accommodation and dinner had been provided for 34 doctors plus one journalist and 6 study staff. Three GPs, 4 study staff and 1 public relations person attended but did not stay overnight. The

overall cost was £215.63 per attendee, including study staff and investigators or £278.01 for delegates. The Panel considered that irrespective of the content, the impression given by holding a half day meeting at the hotel which was a renowned, deluxe venue, including an overnight stay for most delegates, was inappropriate. A breach of Clause 19.1 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. The impression given by the arrangements was such that they brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

A declaration of Pfizer's role in relation to funding the study did not appear on the invitation or agenda or other meeting papers as required by Clause 19.3. Pfizer Inc's observer status was referred to on a slide which discussed the organisation of the study but not the company's financial role. A breach of Clause 19.3 was ruled. The Panel noted that other study material should have similarly contained a clear indication of Pfizer's role. The Panel noted that the only other relevant piece of material before the Panel was the GP template contract which referred to the Pfizer's funding role in the first paragraph. The Panel ruled no breach of Clause 9.10 in relation to the GP template contract.

The only issue to be considered by the Panel in relation to the study was whether it was disguised promotion contrary to Clause 12.2. In this regard particular reference was made in the article at issue to the run-in period. The study was run independently of Pfizer by the university investigators. Nonetheless the Panel considered that in the particular circumstances of this study it was beholden on Pfizer, before it provided the finance, to satisfy itself that the study was not a disguised promotional activity. The protocol stated that the study was powered to demonstrate that celecoxib was not inferior to standard NSAID therapy in relation to CV safety. Eligible patients were subject to a 2 week open-label run-in of treatment with celecoxib. At the end of this period subjects who had taken at least one dose and who did not express a strong preference for either their previous treatment or celecoxib were eligible for randomisation. Appendix 1 to the protocol explained some of the rationale behind the study design and explained that chronic NSAID users who were not taking 'coxib' medicines had demonstrated tolerance to NSAIDs and randomisation without an open phase was thought to introduce a bias in that such subjects would be more likely to tolerate their old medicine than a new one. For this reason the open label phase allowed those who had relatively similar tolerability and efficacy to both therapies prior to randomisation to be included. The Panel noted that the protocol was considered in detail with EMEA and CHMP and was approved by them before recruitment commenced. The Panel did not consider that the points of concern raised in the article at issue were sufficient to demonstrate that the study was disguised promotion. A reasonable explanation appeared in an appendix to the protocol. No breach of Clause 12.2 was ruled.

The Panel noted that given its ruling of no breach of Clause 12.2 it thus followed that given the narrow nature of the allegation in the article that there could be no breach of Clause 18.6 in that Pfizer had funded the study for research purposes and the funding to the university did not constitute an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. No breach of Clause 18.6 was thus ruled.

The Panel noted Pfizer's submission about the modest nature of the payments to practices participating in the study. The practice received a one-off payment of £1,000 to search records and contact patients followed by £5 per month for each participant recruited by the practice and £1 per month for the provision of data in relation to each participant. Given its finding of no breach of Clause 12.2 and noting the level of the payments the Panel considered that the payments were not unreasonable and thus no breach of Clause 18.1 was ruled.

APPEAL BY PFIZER

Pfizer submitted that the study arose from the EMEA's review of the safety of the COX-2 inhibitors, including Celebrex in 2004/5. In June 2005, the CHMP adopted an opinion which required a commitment by Pfizer to undertake a global study to confirm the long term cardiovascular safety of celecoxib. The principal investigator was one of Pfizer's external experts during the review and therefore knew about the CHMP requirement. He subsequently presented a proposed study design which was ultimately accepted by CHMP as suitable in order to meet Pfizer's commitment. It was a large simple trial designed to reflect the real life use of medicines, devised by the principal investigator and his academic colleagues, of a type that he had advocated for many years.

The protocol was drafted by the principal investigator and his academic colleagues and, although it was reviewed and amended by Pfizer and by the CHMP, most of the study documentation was prepared by the principal investigator and his team and the study design remained essentially as those academics had envisaged. The final study protocol was agreed in July 2007. Therefore, whilst Pfizer Inc funded the study, its design was essentially the work of the principal investigator and his academic colleagues, and he was particularly concerned that it should be run independently of Pfizer and that his university would act as sponsor for the purposes of the clinical trials regulations. Pfizer agreed to that arrangement and informed the CHMP accordingly. Pfizer noted that the UK had a particularly strong tradition of clinical research being led, conducted and sponsored by academic institutions and other non-commercial bodies. The study was regarded by the medical and academic community as particularly significant in terms of clinical research nationally and Pfizer's funding as a notable achievement in this regard.

The study contract between Pfizer Inc and the sponsoring university was entered into on 26 July 2007, and the study commenced in January 2008. Under the contract it was clear that the university was the sponsor of the study for the purposes of the clinical trial regulations, and was therefore responsible for the study in regulatory terms, most notably towards the MHRA. The university therefore made the Clinical Trial Application to the MHRA, and received approval to conduct of the study in the UK on 12 April 2007. The university's sponsorship of the study, and Pfizer's funding of it, was made clear in both the study protocol and the participant information sheet, which informed prospective participants that Pfizer, the company which had developed celecoxib, was giving a grant to the sponsoring university to allow this study to be done.

Pfizer submitted that the university and its sub-contractors (mainly other academic institutions) were wholly responsible for the conduct and operation of the study. The contract thus did not require the university or the principal investigator to discuss the study organisation or arrangements with Pfizer, or to obtain Pfizer's approval for the arrangements. The imposition of such requirements would have been inconsistent with the fact that the study was to be conducted independently of Pfizer and with the university's status as sponsor for the purposes of the clinical trials regulations. The running of the study was therefore determined and conducted entirely independently of Pfizer, except that Pfizer representatives might under the contract be invited as observers at meetings of the Executive Committee and had also attended meetings of the Steering Committee as non-voting members. In practice, however, Pfizer was rarely invited to any meetings of the Executive Committee and had not been party to any decisions made by it. However, Pfizer was entitled under the contract to regular updates on the progress of the study via quarterly written reports and, after January 2009, monthly teleconferences. It was important for Pfizer to track the progress of the study given that the conduct of the study was a binding commitment to the CHMP and Pfizer was in turn required to provide updates on the progress of the study to the CHMP.

Pfizer submitted that the meeting on 27/28 March 2009 (and the similar one held on 30/31 January 2009) was initiated and organised by the principal investigator and his team, to inform GPs about the study, with a view to recruit them into it. The study budget set out in the contract with Pfizer allocated funding for all aspects of running the study, including a portion for practice recruitment and initiation meetings. However, the recruitment strategy and arrangements (including the choice of venue) were solely determined and implemented by the principal investigator and the university, as the sponsor of the study. Thus no Pfizer entity knew of the proposals or arrangements for the particular meetings, prior to the meeting held in January 2009. When in February the meeting and venue were first mentioned to the Pfizer Inc study team in the US, they were not familiar with the hotel and it did not therefore trigger any concern. However, once Pfizer UK knew about the March meeting and the planned venue, very shortly before it took place, the concern was raised and Pfizer immediately sought to persuade the principal investigator that the meeting should be held at a different venue. In Pfizer's view the Code did not apply to the university or its meeting, but it was mindful of the view taken of such venues under the Code and the risk that the circumstances of the meeting could be misinterpreted, particularly if the factual background to the study was not known, with consequent potential for reputational damage to Pfizer and the university. The principal investigator strongly objected to Pfizer's communication in this regard and its perceived interference in the logistical arrangements for the study, being entirely outside the company's remit. He declined to change the venue. In the week following the meeting the principal investigator told Pfizer that he before booking the venue he had telephoned the PMCPA, asking whether the Code applied to a meeting held to inform and recruit doctors to a university-sponsored study. He was told that the Code regulated the activities of the pharmaceutical industry and since the university was not the industry and not involved in marketing then the Code did not apply to the university. Pfizer had not been able to obtain any further information about this call; however, it was clear that the principal investigator was satisfied that the Code would not preclude him holding the planned meeting at the hotel.

According to the information provided by the principal investigator to the PMCPA the meeting itself ran from 8.30/9am for a half day on Saturday, 28 March. Thirty seven GPs attended, of which 34 were provided with dinner and accommodation the night before (3 lived locally to the venue). The overall cost was £215.63 per attendee (including study staff and investigators) or £278.01 per delegate (if calculated for GP delegates only). The principal investigator also provided the PMCPA with copies of the invitations, agenda, GCP documents and detailed slide presentations used at the meeting. There was no suggestion in the BMJ article, the Panel's rulings or otherwise that the meeting content was inappropriate or lacked scientific or clinical merit or relevance, or that the costs were excessive. Immediately following the March meeting the principal investigator had made clear to Pfizer his view that it was very difficult to find any other appropriate venue nationally and that the hotel was a cost effective, appropriate option. According to the BMJ article and subsequent correspondence on the topic in the BMJ, it appeared that the university had negotiated a favourable arrangement with the hotel in view of the adverse economic climate, and there was no suggestion or evidence that the hospitality provided was lavish. No leisure/sporting activity or entertainment was provided.

The principal investigator was reported in the article as stating that in his experience doctors were more likely to attend a meeting held on a Saturday than during the week, and it was more cost effective to do

so than to provide attendees with a locum fee of about £350 per day if they had to leave the practice on a working day. In his letter to the BMJ responding to the article he also stated that an evening meeting would not provide sufficient time to thoroughly brief and train GPs on all of the required issues relating to the study. In addition, he explained that since GPs from practices from a wide area were invited, a central venue was necessary, and at the time all other hotel options were more expensive or offered inadequate meeting room facilities or accommodation.

Pfizer submitted that following a number of enquiries from the journalist about the study, the principal investigator invited her to the March meeting at the hotel. His intention (as told to Pfizer when the company queried and objected to his proposals just before it took place) was to demonstrate the scientific value of the study and therefore to fully answer and negate the criticism inherent in her enquiries. The result however (some 5 months after the meeting took place) was the critical article published in the BMJ, which was the subject of this complaint.

The journalist declined the PMCPA's invitation to participate in the complaint procedure. As a result, save to the extent that the matters raised in her article were supported by documentation provided by the principal investigator or were accepted by Pfizer, the journalist's criticisms were unsupported by evidence. In particular the prejudicial comments attributed to unnamed doctors attending the meeting were unsubstantiated and, while the identity of other commentators had been provided, it was unclear what information was provided to them or whether their views were reported in their proper context. Certainly, much of the commentary provided by academics and doctors participating in the study in subsequent correspondence in the BMJ strongly refuted these criticisms. Subsequently, the principal investigator responded to the article in a letter published by the BMJ on 21 October 2009. In his letter he strongly countered the criticisms made in the article.

Pfizer noted that no complaint in relation to the meeting or article was received by the PMCPA or by Pfizer from any health professional attending the meeting or from any other source.

Pfizer submitted that the Panel's ruling was predicated upon its conclusion that the meeting at the hotel to discuss the study was subject to the Code. This, in turn, appeared to be based on its assessment that the study 'was not a strictly arm's length arrangement'. Pfizer disagreed with the Panel for the following reasons:

- While Pfizer was obliged to initiate a long term study to investigate the safety of celecoxib to satisfy regulatory requirements, this did not alter the position that the study was proposed and designed by the investigator/sponsor, that the sponsor was the university and not the company, and that it was agreed by all concerned that the study should be carried out independently of Pfizer. Naturally Pfizer would not have funded this large and expensive study if the company had not wished to obtain the results. However, the fact that Pfizer required the results did not mean it should be viewed as initiating and conducting a study when it was clear that this was not the position.

- As the principal investigator explained in his response to the BMJ article, sponsor had a precise meaning in EU legislation and did not simply mean the funder of the study. Sponsor was defined in the Clinical Trials Directive as 'an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial'. UK academic institutions commonly initiated, led and managed industry funded clinical research. Such research made a vital contribution to the UK science base. In such situations, as in this case, the academic institution might properly be regarded by the regulatory authorities as the sponsor of the study. The university in question had one of the UK's leading medical schools and a particularly strong reputation, worldwide, for medical research.

- Pfizer noted that in relation to any such research of this kind, which was initiated, led and sponsored by an investigator/academic institution, and funded by industry, the investigator's proposed study protocol was commonly, and understandably, reviewed and commented on by the pharmaceutical company concerned. If this was sufficient for the arrangement to be regarded as 'not at arm's length', then this implied that all such research fell within the scope of the Code.

- The Panel's ruling specifically cited the supplementary information to Clause 19.1 of the Code as a reason why the meeting was within the scope of the Code. The third paragraph of the supplementary information referred, inter alia, to training and investigator meetings for clinical trials and non-interventional studies held or sponsored by companies. Pfizer's submitted that this paragraph was not applicable to the arrangements made solely by the principal investigator/the university in relation to the study. The meeting should not therefore be regarded as one to which this paragraph of the supplementary information, and therefore the Code, applied. If the company's funding of the study was sufficient to bring it within the scope of Clause 19.1, then again that would potentially bring into the scope of the Code all meetings for investigator led studies in which the funding companies had, properly, no actual involvement. In Pfizer's view that would have far-reaching and negative consequences for these arrangements between industry and academic institutions.

- The contract between Pfizer Inc. and the

sponsoring university did not require the investigator to comply with the Code, to obtain approval from Pfizer for the arrangements for the study or to permit Pfizer to comment on or contribute to the study documentation. Such control over the investigator and sponsor was inconsistent with the fact that the study was conducted independent of Pfizer and with the role of the university as sponsor of the study. The principal investigator also made clear, when Pfizer sought to persuade him to rearrange the meeting, that control by Pfizer over the organisation of the study was not acceptable to him. As confirmed by the PMCPA in its discussion with the principal investigator, investigators such as himself were not viewed as subject to the Code and while the principal investigator reassured Pfizer that he would comply with applicable laws and regulations, it was not envisaged that the Code could or should control his activities.

- The subsequent action by Pfizer UK in firstly seeking to persuade the principal investigator not to proceed with the meeting at the hotel and subsequently to amend the contract, reflected Pfizer UK's concern (justified by subsequent events) that the meeting could be misinterpreted in view of Pfizer's funding of the study, particularly in circumstances where the full background to the study and its organisation was not available. Pfizer knew about the view taken in relation to such venues under the Code, with the associated possibility of reputational damage to Pfizer and the sponsoring university. When Pfizer UK knew about the meeting and made every effort to persuade the principal investigator to change the venue, he declined to do so believing that the Code did not apply to his meeting and that Pfizer's interference was unwarranted and inappropriate. He told Pfizer at the study team meeting in the week following the meeting that he had considered resigning from the study, such was his objection to Pfizer's stance.

Overall, Pfizer submitted it was incorrect to conclude that Pfizer UK should be responsible under the Code for the meeting held by the principal investigator at the hotel in circumstances where:

a) it was intended by all parties that the study should be conducted at arm's length from Pfizer, the principal investigator insisted that the study should be sponsored by the university and conducted independently of the company and held a strong view, confirmed by his discussion with the PMCPA, that his activities, including the arrangements he made in connection with the study and meetings arranged by him in that context, were not subject to the Code; and

b) the hotel meeting was organised entirely by the principal investigator without reference to or knowledge of the company; Pfizer had no involvement whatsoever in the arrangements or choice of venue and no Pfizer personnel attended.

Pfizer noted that the Panel, in its ruling, recognised uncertainty in relation to the application of the Code to studies such as the one at issue. The Panel accepted that there might be certain activities which fell solely within the investigator's remit on which the company quite properly had absolutely no influence, although it then considered that it was beholden on Pfizer to use its best endeavours to ensure the contract provided that certain activities such as arrangements for meetings, complied with the Code. Pfizer did not understand the distinction suggested by the Panel and suggested that the inference that, in some ways (save for meetings, unspecified) studies such as that at issue might fall within the Code, although in other respects the Code did not apply, was unhelpful. Pfizer and the principal investigator submitted that studies such as the one at issue, where the funding pharmaceutical company had no involvement in the arrangements for the study, should fall outside the provisions of the Code. The Panel's concerns that this would, in some way, permit companies to circumvent the Code were not valid: in circumstances where a company sought to introduce practices contrary to the Code it could not be said that the company had no involvement in the organisation and arrangements for the study and/or meeting. Pfizer submitted that the hotel meeting fell outside the scope of the Code; in these circumstances, the provisions of Clause 19.1 which required that Pfizer certify the materials for meetings attended by health professionals were inapplicable and inappropriate.

However, if the Appeal Board considered that the hotel meeting was subject to the Code, Pfizer made the following submission in relation to the Panel's ruling of a breach of Clause 19.1.

1 The hospitality provided was not, on its facts, lavish or excessive. The amount spent per attendee was reasonable and the Panel did not suggest otherwise. The Panel had expressed the view that an overnight stay for most delegates was inappropriate; however no evidence was available as to the distance travelled by delegates who attended the meeting or whether it would have been difficult for them to get to the venue by 8.30am, without an overnight stay. Such information was not available to Pfizer and the evidence relied upon by the Panel had not been identified. Pfizer noted that some local GPs did not stay overnight, confirming that, in some cases where this was unnecessary, overnight accommodation was not provided. It seemed to Pfizer that delegates would also be more likely to attend a half day meeting on a Saturday than lose a full day of their weekend, and that a relatively early start was therefore necessary. This would be made more convenient and feasible for delegates from outside the immediate area by providing overnight accommodation.

2 The Panel had also criticised the impression given by holding a half day meeting at the hotel which a renowned, deluxe venue. However, the Code provided no absolute prohibition on the use of

five star hotel accommodation and the response to the BMJ article provided by a physician who attended the meeting was that 'there was no golf, spa treatments or any other luxurious indulgence going on'. The Panel's conclusion therefore appeared to be based solely on the impression created by the name of the hotel irrespective of the level of hospitality actually provided. In circumstances where the principal investigator, who chose the venue, expressed the view (which had not been challenged) that a suitable alternative was not available nationally, the arrangements for the meeting should not be viewed as inappropriate.

3 Pfizer was also concerned that the Panel's conclusions regarding the meeting were based on unsubstantiated quotations in the BMJ article. A journalist naturally had an interest in creating a 'story'. In this case, the journalist declined to participate in the complaints process and therefore much of her article was unsubstantiated and should not have been relied upon by the Panel. As indicated above, the accuracy of the quotations referenced in the article was uncertain and it was also unclear what information was provided to the commentators or whether the proper context for the quotations set out in the article had been provided. Such evidence might not properly form the basis for an adverse decision under a fair procedure.

4 A finding that a study such as that at issue was subject to the Code and that the arrangements for a meeting such as that held at the hotel were inconsistent with Clause 19.1 had substantial implications for future similar research in the UK. Large scale studies such as that at issue represented an important means of developing knowledge on use of medicines in a 'real life' context. It was also often viewed as desirable that studies were conducted at arm's length from industry. If, however, industry must control how such studies were organised, scrutinise the associated study material and remove discretion from the study investigators, then in practice this might make it impossible to conduct such research, at least in the UK. It was not a necessary or proportionate response to the requirement to achieve high standards.

Pfizer submitted that as explained above, the hotel meeting and the associated materials provided in the context of that meeting, fell outside the scope of the Code. In these circumstances, the fact that a declaration of Pfizer's role in relation to the funding of the study did not appear on the invitation or certain other meeting papers, as required by Clause 19.3, was not relevant.

The materials prepared for the meeting were not shown to Pfizer at any time. It would not have expected to see such materials as this would have demonstrated company control over the arrangements for the study, inconsistent with this being an investigator initiated study, conducted independently of Pfizer and in circumstances where the sponsor was the university, rather than the company.

Finally, whilst in Pfizer's view the materials for the meeting fell outside the scope of the Code, it was relevant to consider that the purpose underlying Clause 19.3 was to ensure that the industry's involvement in meetings attended by health professionals was transparent. In this case, there was no suggestion in the BMJ article that attendees were unaware of Pfizer's involvement. In fact the article stated that the meeting materials indicated clearly that the study had been requested by the EMEA and that an obligation to conduct such research had been placed on the Celebrex marketing authorization holder. Subsequent correspondence to the BMJ also supported that the participants were well aware of Pfizer's funding of the study, including the principal investigator's statement that 'The financial support of Pfizer for the study was clearly communicated in meeting slides, press releases, and published articles'.

The Panel's ruling of a breach of Clause 9.1 of the Code related to the ruling of a breach of Clause 19.1. The Panel concluded that 'high standards had not been maintained', although no specific explanation for this finding was provided. Pfizer's appeal in respect of the finding of a breach of Clause 19.1 was repeated here. Given that the meeting was not arranged by Pfizer, it had no knowledge of the arrangements and the meeting was, in any event, not lavish, a finding of a breach of Clause 9.1 was, inappropriate. The wording of the Panel ruling made clear that the only criticism of Pfizer was limited to the Panel's view that it was beholden on Pfizer to use its best endeavours to ensure the contract provided that certain activities complied with the Code. Even if, contrary to Pfizer's view, such a criticism had any merit, it did not warrant a finding of a breach of Clause 9.1. That view was given further support by the fact that the PMCPA itself reassured the principal investigator that the Code had no application to his activities.

The ruling of a breach of Clause 2 of the Code related to the Panel's earlier ruling of a breach of Clauses 19.1 and 9.1 arising from the impression created by the meeting held at the hotel, even though the hospitality provided was not lavish. Pfizer submitted that it was significant that the journalist who had written the article, which formed the basis for this complaint, did not view her 'story' as of sufficient interest or urgency to seek early publication and her allegations were followed by correspondence refuting her criticisms. The journalist declined to participate in the PMCPA investigation, to support the allegations made in the BMJ article. No other complaints from the health professionals attending the meeting or otherwise, or from any other source, had been received arising from this event. In these circumstances, it was simply incorrect to conclude that the meeting resulted in any genuine concern or criticism from anyone who knew the full facts.

Pfizer strongly believed that this case did not fall within the scope of Clause 2. The study was and continued to be run independently of Pfizer and the company had no involvement in the arrangements. In circumstances where Pfizer, concerned that the meeting could be misinterpreted, urged the principal investigator to rearrange the venue, but could not prevent the meeting proceeding and the PMCPA itself advised the investigator that his activities were not subject to the Code, a finding that particular censure of Pfizer's actions was required was wholly inappropriate. Pfizer referred to three other cases since 2006 which had included rulings of a breach of Clauses 2, 9.1 and 19.1 but were readily distinguished from the meeting at issue (Cases AUTH/1827/4/06, AUTH/1848/6/06 and AUTH/1745/7/05). Pfizer submitted that the ruling of a breach of Clause 2 related to certain of the meetings, namely a visit to a lap-dancing club and an event at Wimbledon. In all cases, hospitality/payments to journalists were offered by or on behalf of a company in respect of matters that were clearly subject to the Code and which constituted obvious breaches of its provisions.

Whilst Pfizer maintained that the hotel meeting should not be viewed as subject to the Code, it was significant that other cases where comparable levels of hospitality had been provided (eg Case AUTH/2068/11/07) did not result in a ruling of a breach of Clause 2 even though the hospitality was clearly subject to the Code, was arranged with the full knowledge of the relevant company and was comparable or more lavish than that provided in this case and where there was no indication that the company made the efforts recorded in this case to alter the arrangements.

In summary, Pfizer submitted that the Panel's rulings appeared to be based on allegations or comments contained in the BMJ article, in circumstances where the journalist had an interest in writing a 'story' and declined to participate in the complaints procedure. Save to the extent that matters of fact in relation to the hotel meeting had been substantiated, the article should not be regarded as determinant. Reliance upon unsupported allegations/comments by third parties to form the basis of an adverse decision was inconsistent with a fair procedure. The case raised important points of principle in relation to the extent to which a company should control the arrangements for independent, investigator initiated trials in the UK where the company only provided funding and was not the sponsor. The fact that this case represented new ground for the PMCPA was demonstrated by the lack of previous cases with comparable facts. Pfizer sought only arm's length involvement in the study and did not wish to influence arrangements made by the investigator - an approach viewed by the investigator, and the university sponsor, as critical. Pfizer played no part whatsoever in the arrangements for the meeting. In these circumstances, the study and the meeting should not be viewed as subject to the Code. That view was confirmed by the PMCPA in a discussion with the principal investigator, which he stated took place before he confirmed the arrangements for the meeting.

Pfizer alleged that the arrangements for a meeting such as that held at the hotel should be a matter for the investigator/sponsor of the study and that it was inappropriate for a company such as Pfizer to seek to influence the conduct of a study conducted independently of industry. Furthermore, in this case it was relevant that the investigator strongly defended his choice of venue and that it was, on the facts, not lavish or inappropriate in any way. The sole criticisms of the venue appeared to relate to the name of the hotel and in considering whether it was appropriate to hold the meeting at this site, and no account appeared to have been taken of the limited alternatives available.

In summary, Pfizer submitted that on the particular facts of this case, the meeting at the hotel should not be viewed as falling within the Code and therefore all of the Panel's rulings fell away. If, contrary to Pfizer's position, the meeting was subject to the Code, Pfizer's conduct, specifically its lack of any involvement in the arrangements for the meeting and its efforts to persuade the investigator to change the venue, meant that breaches of Clause 9.1 and 2 should not be found. Such findings would dilute the significance of breaches of those clauses to an extent that prejudiced their value as a deterrent.

APPEAL BOARD RULING

The Appeal Board noted Pfizer's submission and the comments of the principal investigator about their respective roles and responsibilities in relation to the study. The Appeal Board considered that it was important to note the regulatory requirement for the study. The EMEA had reviewed the safety of the COX-2s, including Celebrex in 2004/5. In June 2005 the CHMP recommended the maintenance of the marketing authorization for Celebrex on the basis that Pfizer initiated a global study to investigate the long term cardiovascular safety of celecoxib relative to non-selective NSAIDs. The Appeal Board noted that the BMJ article commented on the role of the principal investigator. The Appeal Board noted Pfizer's submission that he acted as an external medical consultant on celecoxib for Pfizer Inc including attending the Oral Explanation before the CHMP on Pfizer's behalf and it was in this capacity that he was aware of the CHMP requirement for a study and became involved. Pfizer had initially planned to sponsor the study which it submitted was the more usual approach. However, the principal investigator presented a proposed study design which was ultimately accepted by CHMP as suitable in order to meet Pfizer's regulatory commitment. The protocol was reviewed and amended by Pfizer and the CHMP.

The study agreement stated that the university was the study sponsor for the purposes of the clinical trial regulations and Pfizer provided the funding. The university undertook to keep Pfizer updated on progress at regular intervals and provide quarterly

written reports on the study progress in terms of enrolment, study centre rollout and other material issues arising in relation to the study. Pfizer Inc personnel were permitted to attend meetings of the Executive Committee and the Steering Committee as non voting observers. Pfizer's attendee's at these meetings had been epidemiologists. After January 2009, monthly teleconferences were also held with Pfizer.

The Appeal Board was concerned that the first time Pfizer UK heard about the meeting at issue was when it was contacted by a journalist who wished to attend the meeting which was held in the UK and thus potentially subject to the UK Code (as set out in the supplementary information to Clause 1.7). UK health professionals had attended the meeting.

The Appeal Board noted that once it knew about the meeting in the hotel Pfizer had contacted the principal investigator and requested that the venue be changed as there was a high likelihood of Pfizer being associated with it. However, the university proceeded with the arrangements. Pfizer submitted that it was unable to prevent the meeting taking place and that it had no legal control over the meeting.

The Appeal Board noted from the study agreement that £170,000 was set aside for practice recruitment and initiation meetings for each of the first two years. The Appeal Board was concerned about Pfizer's lack of control or even guidance about how this money was to be used.

The Appeal Board acknowledged that investigator initiated studies made an important contribution to knowledge about medicines and their use. Whether or not they were subject to the Code would depend on the circumstances of each particular case. The fact that some of these studies might be subject to the Code did not, in itself, mean that they could not happen. Each case would be considered on its own particular merits.

The first matter to be decided in this case was whether Pfizer was responsible under the Code for a study it had funded and which was undertaken to satisfy regulatory requirements and maintain Celebrex's marketing authorization. The Appeal Board noted that given the regulatory requirement for the study funded by Pfizer the description used by Pfizer, 'investigator initiated' did not give a wholly accurate impression of the process by which the study was devised.

Pfizer's representatives at the appeal hearing advised that as of July 2009 the regulators released Pfizer from its regulatory commitment to complete the study. Nonetheless, the study was currently continuing. Although of interest this was not relevant to the Appeal Board's consideration as when the meeting in question took place, the regulatory requirement was still in force.

The Appeal Board noted that when approving protocols etc for company-funded studies regulators imposed certain obligations upon those companies particularly, for instance, with regard to the collection of adverse event data. The mere fact that a company acted to fulfil its obligation in this regard in what was otherwise a wholly independent study did not necessarily mean that the study could not be considered to be conducted at arm's length. Taking all the circumstances into account the Appeal Board decided that although Pfizer funded the study there was a high degree of independence built into it. The Appeal Board decided that Pfizer was not responsible under the Code for the arrangements at the investigator's meeting in the hotel. These were the responsibility of the university. The Code did not apply and thus there could be no breach of it. The appeal was successful.

Notwithstanding its ruling above that the arrangements at the investigator's meeting in the hotel were not covered by the Code, the Appeal Board was very concerned about the perception of such meetings and their possible adverse effect upon the reputation of the pharmaceutical industry. The Appeal Board was also concerned that the materials circulated for the meeting, including invitations to potential investigators, did not mention Pfizer's role as funder of the study. It considered that, in their contracts with study sponsors, companies would be well advised to at least refer to the requirements of Clause 19 in relation to meetings and to transparency in relation to the involvement of the company even if the arrangements, as here, were not subject to the Code.

Proceedings commenced	**9 September 2009**
Case completed	**24 March 2010**

GENERAL PRACTITIONER v CHIESI

Conduct of representative

A general practitioner complained about the sales pressure exerted by a Chiesi representative to get his practice to switch asthma patients to Fostair (beclometasone plus formoterol); this had been ongoing for most of the year. At a meeting in September 2009 attended by another doctor, two practice nurses and the complainant, the representative gave misleading and false information regarding other local practices' activities. The representative stated that two other practices were already making switches and that the local primary care trust pharmacy representatives were keen to see switches undertaken. Neither statement was true.

The detailed response from Chiesi is given below. There was some exchange of submissions between the parties before the Panel made its ruling.

The Panel noted that the parties' accounts differed; it was difficult in cases involving discussions between a representative and a health professional to know exactly what had transpired. There had been significant delays in obtaining more information from the complainant who had waited to discuss the matter with several colleagues. A judgement had to be made on the available evidence bearing in mind the extreme dissatisfaction usually necessary on the part of an individual before he or she was moved to submit a complaint.

In the Panel's view it was beholden upon representatives to be very clear when discussing other health professionals' use of a product so as not to mislead by implication. The complainant consistently maintained that he and others had been misled in that regard. In addition there appeared to be confusion about whether Chiesi was supporting disease reviews or switches of products. However, the complainant had the burden of proving his complaint on the balance of probabilities. The Panel considered that on the basis of the evidence provided by the parties it was impossible to know exactly what had been said to whom. In the circumstances the Panel ruled no breach of the Code.

A general practitioner complained about sales pressure, on going for most of the year, exerted by a representative from Chiesi Limited to get his practice to switch asthma patients to Fostair (beclomethasone plus formoterol).

COMPLAINT

The complainant stated that at a meeting in September attended by another doctor, two practice nurses and the complainant, the representative gave misleading and false information regarding other local practices' activities. The representative stated that two other practices were already making switches and that the local primary care trust (PCT) pharmacy representatives were keen to see switches undertaken. The complainant submitted that neither statement was true.
The complainant had discussed this situation with the other doctor and the PCT pharmacy team and they had encouraged him to complain to the Authority.

When writing to Chiesi, the Authority asked it to respond in relation to Clauses 2, 7.2, 9.1 and 15.2 of the Code.

RESPONSE

Chiesi stated that in July 2009, the representative gave a presentation on Fostair at a practice-based commissioning (PBC) group meeting, of which the complainant's surgery was a member. At this meeting, the chair of the PBC group and recommended the use of Fostair within the group and told the representative that he would submit a formulary inclusion for Fostair to the area prescribing committee. The practice manager at the complainant's surgery subsequently organised a meeting for September 2009, at which the representative could discuss Fostair with the GP partners and look at the possibility of reviewing some patients who were on other products to see if they would be suitable for Fostair.

In August 2009, the representative met a practice-based pharmacist who looked after the PCT. The pharmacist was open to discussing a disease review which had been completed at another surgery which was part of another PBC of which the pharmacist had oversight.

Chiesi submitted that at the September meeting with the representative the practice manager was particularly interested in any potential cost savings for the surgery. The representative explained that two nearby surgeries (which were part of the same PBC) had started to undertake disease reviews and that work was ongoing. The representative knew of these through conversations with the medical staff at these two surgeries. The practice manager then suggested that the representative tell the complainant about these ongoing projects. Chiesi stated that as its representative did not know if those reviews had resulted in any patients being prescribed Fostair, there could be no suggestion that any changes in products were happening as stated by the complainant.

At 1.15pm on the same day the representative met a GP at the complainant's surgery, using Fostair material. The GP agreed with Fostair's clinical and cost saving benefits. The representative told the GP about the agreed actions resulting from the July meeting that the Chair of the PBC had stated that he would submit Fostair to the area prescribing committee for formulary inclusion. Chiesi noted that this formulary inclusion was at a PBC level and not at the PCT level as stated by the complainant. Fifteen minutes later the complainant joined the discussion. He seemed surprised that the representative was at the surgery but she explained that the meeting was to discuss Fostair with the GP partners and nurses as agreed with the practice manager. The representative then updated the complainant on what was happening at the other two nearby surgeries (part of the same PCT) and their projects on reviewing patients. The representative also referred to the above mentioned practice-based pharmacist, and told the complainant that a surgery where the pharmacist worked had also decided to review patients and that the pharmacist would have been familiar with the process involved. Again, the representative would not be able to say if medicine had been changed as she was not aware of any patients having been reviewed and then initiated onto Fostair. The complainant stated that he would have preferred to have had some experience of Fostair before using more of it and the representative agreed.

Chiesi's submitted that the representative saw the complainant three times in 2009, once at the PBC group meeting as mentioned above, once at a face-to-face appointment and latterly at the meeting in September, and therefore the complaint about the representative's sales pressure to get the surgery to change product for most of 2009 was a surprise.

Chiesi regretted the misunderstanding with the complainant but considered that the representative had neither given misleading or false information, nor failed to maintain high standards. Chiesi thus denied breaches of Clauses 2, 7.2, 9.1 and 15.2.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant had discussed the matter with the local pharmacy advisor and various members of the PBC group. The pharmacy advisor recalled that in August it was stated that until Fostair was approved by the area prescribing committee she would not recommend its use. The pharmacy advisor was also told by the representative that another local practice was going to switch to Fostair; she followed this up with the practice concerned and found this not to be the case but that Chiesi was doing work looking at switching patients from Beclazone to Clenil. The final comment from the pharmacy advisor was 'I think this representative purposefully confused people by not being clear about the difference between reviews being carried out in practice eg poorly controlled asthma patients and implied that these were actually reviews looking at drug switching to Fostair'. The PBC considered that the representative had used undue sales pressure to get her product prescribed. The chairman had informed the complainant that Fostair was not on the area prescribing committee formulary – the committee had requested further appraisal of the product by one of the local respiratory physicians. There was only a limited amount of prescribing of Fostair locally.

FURTHER COMMENTS FROM CHIESI

Chiesi noted that the complainant originally referred to a meeting between himself and a representative in September and although Chiesi's response was sent to the complainant for comment. The complainant did not comment upon it or refer to his original complaint Chiesi thus assumed that the complainant had accepted the company's explanations. Chiesi noted that in his further comments the complainant referred to another meeting in August 2009 and also mentioned an un-named pharmacy advisor and an un-named local practice as the source of his second complaint.

Chiesi submitted that it was not possible for the company to investigate the second complaint in a thorough manner as it did not know the name of the pharmacy advisor or the local practice.

Representatives interacted with many customers a day and it was not possible to establish with absolutely certainty who the complainant had referred to without a name. All the company had to go on was a specific date in August; was that date correct? Chiesi requested a name so that it could question its representative more closely. Chiesi noted that the complainant had now complained on behalf of a pharmacy advisor. It had not been verified if the pharmacy advisor had a complaint to make or if she wanted to make a complaint. As a health professional in her own right, if the pharmacy advisor had a complaint to make, would she not have made it herself? Chiesi further noted that the complainant was not at the meeting in August and therefore his latest complaint was based on secondary sources.

Taking all the above into account, Chiesi considered that there was no *prima facie* case to answer with regard to the complainant's second complaint.

Chiesi noted that there was a common theme running through both submissions from the complainant, which was about the representative's sales pressures to get a practice to switch asthma products and that the representative had used undue sales pressure to get her product prescribed.

In response to a request for further information Chiesi stated that its representative did not see any customer bearing the title of pharmacy advisor on that date in August.

FURTHER COMMENTS FROM THE COMPLAINANT

In response to a request for further information the

complainant provided a statement from a local practice support pharmacist who stated that she had met the Chiesi representative on the date in August. The meeting was not pre-arranged but the practice manager asked her to talk to the representative about the work the representative was doing in the practice. It was at that meeting that the pharmacist was told that certain local practices would be switching to Fostair. The pharmacist subsequently discovered that that information was not true.

FURTHER COMMENTS FROM CHIESI

Chiesi confirmed that following an introduction by the practice manager, its representative had spoken to the practice support pharmacist. Two local practices were referred to in that conversation: one where only the use of Clenil was discussed and the second where the representative stated that one of the GP partners would raise Fostair for discussion at the next PBC committee meeting. However the use of Fostair at this practice was not discussed.

Chiesi noted that in the six months until August 2009 the two practices prescribed between 20 and 30 units of Fostair each.

PANEL RULING

The Panel noted that the parties' accounts differed; it was difficult in cases involving discussions between a representative and a health professional to know exactly what had transpired. There had been significant delays in obtaining more information from the complainant who had waited to discuss the matter at a PBC group meeting as well as contacting others. A judgement had to be made on the available evidence bearing in mind the extreme dissatisfaction usually necessary on the part of an individual before he or she was moved to submit a complaint.

In the Panel's view it was beholden upon representatives to be very clear when discussing other health professionals' use of a product so as not to mislead by implication. The complainant consistently maintained that he and others had been misled in that regard. In addition there appeared to be confusion about whether Chiesi was supporting disease reviews or switches of products. However, the complainant had the burden of proving his complaint on the balance of probabilities. The Panel considered that on the basis of the evidence provided by the parties it was impossible to know exactly what had been said to whom. In the circumstances the Panel ruled no breach of Clauses 2, 7.2, 9.1 and 15.2.

Complaint received **16 September 2009**

Case completed **30 April 2010**

ALCON LABORATORIES v ALLERGAN

Retrospective rebate scheme

Alcon alleged that a scheme whereby Allergan contractually granted NHS organisations retrospective cash rebates in relation to the prescription of the company's eye drops for glaucoma was an inducement to prescribe, recommend and buy Allergan's products. The scheme did not fall within the exclusion in the Code for measures and trade practices relating to prices, margins and discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993. Further, the scheme might subvert the ability of participating NHS organisations to form their own opinion of the therapeutic value of Allergan's glaucoma medicines; the scheme did not comply with high standards and it compromised the interests of glaucoma patients, and thus brought discredit upon, or at least reduced confidence in, the pharmaceutical industry.

The scheme granted cash rebates if the value of Lumigan, Ganfort and Combigan prescribed and dispensed within a defined geographic area met certain unit market thresholds, calculated as a percentage of the total market for glaucoma medicines. If a participating organisation achieved the lowest threshold then the lowest rebate rate would be paid. Two further, higher thresholds triggered the payment of higher rebate rates to a set maximum. The cash refund was paid into a separate fund managed by a fund management executive (typically three NHS employees) which governed spending of the fund. The stated intended purpose of the scheme was: '...to develop ophthalmic services in the community and or for the benefit of patients with ophthalmic conditions'. No payments to individuals were permitted (unless such payment went through the NHS payroll – for example, the fund could be used to employ a nurse).

Alcon was concerned that in its practical effect, the scheme unacceptably compromised prescribers' discretion to prescribe the most appropriate product for each patient.

Even in areas where the unit market share of Allergan's products was already around the lowest percentage required to trigger the scheme, prescribers would have to substantially increase the number of prescriptions for Allergan products (based on average market shares in the absence of any such scheme) in order to obtain the higher rebate rates which NHS organisations would naturally aim for.

The real issue was by how much Allergan's market share must increase in order to reach the required threshold to obtain the rebate ie, how many patients would be irrationally switched from a non-Allergan product to an Allergan product as a consequence of the scheme. The glaucoma market grew slowly (approximately 4% - 5% per year) with very few new entrants, and so the only way to increase market share was to decrease the share held by competing products by switching.

Allergan's attempt to dissociate itself from the potential negative effects of the scheme by arguing that whether any participating trust chose to adopt a strategy to maximise its rebate was outside of its control was disingenuous; it appeared that the scheme in itself incentivised participating trusts to adopt strategies to maximise their rebate which Alcon believed would inappropriately compromise clinicians' freedom to prescribe the most appropriate product to patients.

The risks associated with the scheme would be even more pronounced in certain areas where more than one organisation enrolled in the scheme would compete with others in the same area to meet the thresholds required to obtain the rebate. As an organisation would not know what threshold had been achieved by the other NHS organisation(s) in that area, it was likely to over-compensate by adopting strategies to significantly increase its own unit market share for Allergan products so that it was best placed to obtain the rebate itself.

Alcon gave a detailed account of its objections to the scheme which it considered sought to distort the market and incentivise NHS organisations to reach an unreasonable goal which might not benefit the NHS in the long-run.

Alcon considered that in seeking to attain the requisite thresholds for the grant of the rebate, NHS organisations might lose sight of the therapeutic value of Allergan's medicines such that they were prescribed irrationally, instead of as one possible product amongst an appropriate range of options.

Irrespective of whether the scheme was an inducement, Alcon considered that it did not maintain high standards because it promoted Allergan's products at the expense of good medical practice and incentivised NHS organisations to get rid of other glaucoma medicines, which compromised the interests of patients.

Alcon considered that irrespective of whether the scheme was an inducement to prescribe/recommend/buy Allergan's products it

brought discredit upon, or at the very least reduced confidence in, the pharmaceutical industry.

Alcon did not believe that the application of Clause 2 was avoided on the basis that the purpose of the scheme was to develop community ophthalmic services and/or benefit patients with ophthalmic conditions. Whilst there might be an overall benefit to ophthalmic patients generally, this might be at the expense of individuals who were denied the most appropriate product for their condition. Further, the scheme agreement specifically stated that: '... the fund management executive may decide to use the fund for purposes indirectly linked to ophthalmic patients or service development'. Therefore, it was not guaranteed that there would be any benefit at all to ophthalmic patients, let alone the glaucoma patients who were directly affected by the scheme.

The detailed response from Allergan is given below.

The Panel noted that Allergan described the scheme as a commercial agreement relating to discounts through rebates between Allergan and either a national health trust, NHS health board or an NHS practice based commissioning organisation. The retrospective rebate scheme agreement set out the terms of the rebate agreement, the accumulation of the rebate community fund and the use of the fund. According to the agreement the rebate was paid on the achievement of unit market share thresholds within the period of the agreement (12 months) applied to the value of a range of prescribed and dispensed Allergan ophthalmic medicines. The rebate was paid as a cash fund retrospectively on a quarterly or annual basis into the NHS organisation's business account. Before signing the agreement a fund management executive was appointed comprising three NHS employees. The agreement stated that the fund was intended to be used to develop community ophthalmic services and/or for the benefit of patients with ophthalmic conditions. However this was not an exclusive requirement – the fund management executive could decide to use the fund for purposes indirectly linked to ophthalmic patients or service development. Allergan would not influence or attempt to influence the use of the rebate fund. The agreement could only be cancelled early by mutual consent.

The powerpoint presentation 'B2B [business to business] Retrospective Discount Scheme' stated that to work within the Code the accrued cash fund would be treated as a separate trust-fund administered by a committee of stakeholders to manage and agree on the use of the fund which would be available to purchase products and services which would be recorded for audit. The Panel noted that the presentation was not wholly consistent with the agreement on this point.

The Panel noted that the Code excluded from the definition of promotion measures or trade practices relating to prices, margins or discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993. Further the supplementary information to the Code stated that such measures or trade practices were excluded from the provision of that clause. Other trade practices were subject to the Code. The terms prices, margins and discounts were primarily financial terms.

The Panel noted that the Allergan scheme linked primary care prescribing volumes to a product where prescribing was usually initiated in secondary care. The agreement at issue covered both the cash rebate and the administration of the subsequent trust fund. The Panel considered that the establishment of a managed trust fund wherein cash accumulated was an integral part of the retrospective rebate scheme. Allergan had provided no evidence that such composite schemes were in regular use by the pharmaceutical industry prior to 1 January 1993. The Panel considered that such composite schemes could not take the benefit of the exemption. The scheme was thus subject to the Code.

The Panel noted that the agreement set out a loose framework for the establishment and operation of the rebate fund. According to the agreement Allergan would not influence or attempt to influence the use of the fund nor was it represented on the fund management executive. Fund managers would be given a monthly statement on the fund accrual. Monies would be paid quarterly or annually.

The Panel noted Alcon's allegation that the scheme operated as an inducement to prescribe Allergan's products contrary to the Code. The Panel noted the relationship between national unit share of Allergan's promoted portfolio, the market share in the majority of areas and/or NHS organisations and the threshold unit market share required to trigger the scheme. In that regard the Panel assumed that many areas would have to increase their prescribing of Allergan's products in order to reach the first threshold and thus qualify for a rebate. Four areas had signed up to the scheme of which two had unit shares above the first threshold, one above the second threshold and one just below the first threshold. The Panel considered that insofar as the scheme encouraged the trust to persuade prescribers to increase their prescribing so that the trust could gain a cash rebate, or increase its cash rebate, it could be interpreted as an inducement. The Panel noted that the Code related to inducements to individuals rather than organisations. The Panel considered that the scheme did not operate as an inducement to individuals nor was there evidence that payments had been made from a rebate fund to individuals as an inducement to prescribe or recommend Allergan's medicines contrary to the provisions of the Code. No breach was ruled

The Panel did not consider that the scheme was such that it made claims about the therapeutic

value of Allergan's medicines. In that regard the scheme was not such that it would prevent prescribers from forming their own opinion of the therapeutic value of the medicines. No breach of the Code was ruled.

The Panel noted the intended purpose of the rebate fund as set out in the Retrospective Rebate Scheme Agreement, namely to directly or indirectly develop ophthalmic services in the community and/or for the benefit of patients with ophthalmic conditions. The Panel considered that the rebate scheme in effect could be seen as a donation, grant or benefit in kind and should thus comply with the Code. The Panel noted that in the representatives' briefing document in a section entitled 'Actions to get started', step one involved the identification of hospitals with a market share above a stated percentage. The formulary status of all three glaucoma products in the hospital had to be determined and if one or more were not in the formulary immediate action was to be taken to gain formulary listings and also a special prices offer to the hospital pharmacy for all three glaucoma products must be made. Further, once the agreement had been signed the territory manager would support participating units with appropriate educational events and meetings. It thus appeared that a package of support was provided to the NHS organisation in addition to the cash rebate. The Panel considered that the provision of the cash rebate as a donation, grant or benefit in kind to the NHS organisation was inextricably linked to the promotion of Allergan's glaucoma medicines such that it amounted to an inducement to prescribe, supply, administer, recommend or buy such medicines contrary to the Code. A breach of the Code was ruled. High standards had not been maintained. A breach of the Code was ruled.

The Panel was concerned that the arrangements were such as to bring discredit upon or reduce confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Upon appeal by Allergan the Appeal Board considered that although the scheme at issue contained elements of trade practices relating to prices, margins and discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993, and which were otherwise exempt from the Code, the way in which the scheme operated as a whole meant that it had gone beyond that exemption and was thus subject to the Code.

The Appeal Board noted that the scheme was based upon a volume based percentage market share ie the amount of rebate due depended upon the number of bottles of Allergan products prescribed. The Appeal Board further noted that the representatives' briefing material stated that the territory managers would support participating units with appropriate educational events and meetings. Alcon confirmed at the appeal that it had no evidence to show that the provision of educational events and meetings was exclusively linked to the retrospective rebate scheme.

The Appeal Board considered the applicability of the Code and noted that in its view the rebates paid were a contractual financial arrangement. The amount paid was conditional on obtaining certain thresholds of market share. In that regard the Appeal Board did not consider that the rebate was a medical and educational good or service in the form of a donation, grant or benefit in kind. The Appeal Board thus ruled no breach of the Code.

The Appeal Board was concerned that the scheme could be perceived as an inducement to prescribe Allergan's products. The Appeal Board noted that generally such schemes might result in more prescriptions of a company's product. That was not necessarily unacceptable as long as the arrangements complied with the Code. The question to be established was whether the scheme amounted to an inappropriate inducement. A primary care organisation would potentially qualify for a larger cash rebate if its prescribers increased the number of packs of Allergan products they prescribed. Whilst it was true that one way to do this would be to switch from another company's medicines, nonetheless, the Appeal Board noted that there was no evidence of undue pressure on individual prescribers to do this. On the merits of this particular case the Appeal Board decided that Allergan had not failed to maintain high standards. No breach of the Code was ruled. The Appeal Board subsequently ruled no breach of Clause 2. The appeal was successful on all points.

Alcon Laboratories (UK) Limited complained about a retrospective rebate scheme operated by Allergan Ltd in relation to its medicines for glaucoma (Lumigan, Combigan and Ganfort). Inter-company dialogue had been unsuccessful.

COMPLAINT

Alcon noted that Allergan had contractual agreements with various NHS organisations, including primary care trusts (PCTs), such that they were granted retrospective cash rebates in relation to the prescription of Lumigan, Combigan and Ganfort (the 'scheme'). Alcon alleged that the scheme was an inducement to prescribe, recommend and buy Allergan's products contrary to Clause 18.1 of the Code and Regulation 21(1) of the Medicines (Advertising) Regulations 1994, or in the alternative Clause 18.5 of the Code. Alcon did not consider that the scheme fell within the exclusion for measures and trade practices relating to prices, margins and discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993. Further, the scheme contravened Clause 7.2 because it might subvert the ability of participating NHS organisations to form their own opinion of the therapeutic value of Allergan's glaucoma medicines; Clause 9.1 because the scheme did not

comply with high standards and Clause 2 because it compromised the interests of glaucoma patients, and thus brought discredit upon, or at least reduced confidence in, the pharmaceutical industry.

Alcon stated that Allergan had approached different ophthalmic departments in the UK, proposing that they signed up for the scheme. Alcon provided a copy of the Retrospective Rebate Scheme Agreement that it believed certain NHS organisations had signed, together with a copy of a slide presentation that it understood Allergan used to promote the scheme.

NHS organisations participating in the scheme were granted cash rebates if the value of Lumigan, Ganfort and Combigan prescribed and dispensed within a defined geographic area met certain unit market thresholds, calculated as a percentage of the total market for glaucoma medicines. For example, in order for an NHS organisation to obtain the lowest rebate rate then a pre-set percentage of all glaucoma prescriptions within a certain area must be for Allergan's products.

The rebate fund might be accessed on a quarterly or annual basis and the period of the agreement was one year. A fund management executive (typically three employees of the NHS) would have sole access to the fund and governed spending of the fund. No payments to individuals were permitted (unless such payment went through the NHS payroll – for example, the fund could be used to employ a nurse).

Alcon was concerned that in its practical effect, the scheme unacceptably compromised prescribers' discretion to prescribe the most appropriate product for each patient, and encouraged irrational switching. This was of particular concern in the context of glaucoma medicines because it was often arbitrary as to why a patient responded better to one than another with regards to efficacy and tolerance. It was therefore crucial that prescribers were not inappropriately fettered in their prescription choices.

According to Allergan, 'The thresholds [required for obtaining the rebate] are specifically set at a low level of unit share so that clinicians maintain the freedom to prescribe the most appropriate product for each patient'. Thus, it seemed that Allergan agreed that unless the market share thresholds were indeed set at an appropriately low level, clinicians' freedom to prescribe the most appropriate product for each patient would be compromised.

However, Allergan had not substantiated what it meant by a 'low level of unit share'. Alcon provided a table of data to show that a minimum threshold was set to trigger the scheme and as unit market share increased then so did rebate to a fixed maximum. Clearly, the unit market share required to trigger the payment of the rebate could only be low as relative to the unit market share in the absence of any such scheme. However, from the example set out in Allergan's slide presentation for one particular defined area which relied on figures between September 2007 and February 2008, it was clear that the unit market share for Allergan's products was well below the percentage required to trigger the scheme.

Alcon submitted that to obtain the lowest rebate, some NHS organisations would have to increase the number of prescriptions of Allergan products in order to meet the unit market share threshold. Even in areas where the unit market share was already around the threshold value for Allergan's products, prescribers would have to substantially increase the number of prescriptions for Allergan products (based on average market shares in the absence of any such scheme) in order to obtain the higher rebate rates which NHS organisations would naturally aim for.

In inter-company dialogue, Allergan had declined to state what level of unit share it considered to be low in terms of the difference between the unit market share required to obtain the rebate and the current market share held by Allergan in the areas concerned. Allergan had implied without adequate justification that it believed that the unit market share threshold was low, but Alcon was not satisfied that this was the case. Allergan's comment about the market share threshold and the number of other patients that could still be prescribed other products was misleading. The real issue was by how much Allergan's market share must increase in order to reach the required threshold to obtain the rebate - in other words, how many patients would be irrationally switched from a non-Allergan product to an Allergan product as a consequence of the scheme. The glaucoma market was subject to slow growth (approximately 4% - 5% per year) with very few new entrants, and so the only means of increasing market share was to decrease the share held by competing products by switching. Allergan's own example in its slide presentation indicated that the current unit share for its glaucoma products was well below the first threshold in certain areas. Further, Allergan referred only to the lowest threshold in an attempt to justify the scheme – but NHS organisations would naturally aim for the highest rebate rate which meant that Allergan's products would have to attain a greater market share in the area concerned. Alcon inferred from Allergan's silence on the issue that it did not adjust the unit market share thresholds under the agreement in order to ensure that they were realistic for each participating NHS organisation. For example, it seemed that the same unit market share threshold targets were imposed on each participating NHS organisation, irrespective of geographical differences in Allergan's market share in the absence of any such scheme.

Whilst the scheme was not primarily designed as a switch scheme, Alcon believed Allergan intended to encourage a switch from competitor products as this was the only way to increase its own market

share. Allergan's attempt to dissociate itself from the potential negative effects of the scheme by arguing that whether any participating trust chose to adopt a strategy to maximise its rebate was outside of its control was disingenuous; it appeared that the scheme in itself incentivised participating trusts to adopt strategies to maximise their rebate which Alcon believed would inappropriately compromise clinicians' freedom to prescribe the most appropriate product to patients.

Although Alcon understood that the scheme was structured such that, generally, there would be only one NHS organisation participating in a particular area, there would be cases where more than one was participating in the scheme in a particular area (eg London). The risks associated with the scheme would be even more pronounced in such cases as this would mean that the organisations would be competing with each other to meet the thresholds required to obtain the rebate. As a particular organisation would not be certain as to what threshold had been achieved by the other NHS organisation(s) in that area, it was likely to over-compensate by adopting strategies to significantly increase its own unit market share for Allergan products so that it was best placed to obtain the rebate itself.

Further, although the scheme agreement was for one year in all cases, participating NHS organisations might elect to receive fund payments on a quarterly or annual basis. Allergan's slide presentation explained that an annual payment would be larger than four quarterly payments as a consequence of exponential growth of the fund. NHS organisations would therefore be encouraged to accept annual payment. Even though Allergan would, in any event, provide quarterly reports showing unit market share, the consequence of accepting annual payment was that participating NHS organisations might be tempted to prescribe even more Allergan products than was necessary to obtain the rebate on the basis that the accounting period was longer, and there was therefore greater uncertainty. Accordingly, for those NHS organisations which elected for annual payment (which Alcon anticipated would be the majority), the effects of the scheme would be even more pronounced.

Finally, for the sake of completeness Alcon added that it did not understand the relevance of Allergan's comment that: '...hospitals are today...awarding single product tenders that remove prescriber choice very significantly and yet, provided the NHS believes several different products meet the same clinical need, this is not viewed as objectionable'.

A tender procedure, under which a range of products was assessed for clinical/cost effectiveness according to defined criteria, was very different to a unilateral approach by a pharmaceutical company which sought to incentivise NHS organisations to buy/recommend its products. Allergan also likened the scheme to a patient access/risk sharing scheme (many of which had been taken into account by the National Institute for Health and Clinical Excellence (NICE) in its assessments of cost effectiveness). However, the objective of the scheme was very different from that of a patient access scheme whereby the price paid for a medicine was fully or partially refunded if the outcome of the use of the medicine in a patient failed to meet certain criteria. In any case, Alcon understood that risk sharing/outcome guarantee schemes fell outside the scope of joint working and must be reviewed in accordance with the Code. Alcon maintained its arguments for a breach of the Code.

Breach of Clause 18 – inducement to prescribe

The scheme operated in such a way that each prescription of a non-Allergan product was a potential obstacle to obtaining the rebate. Therefore, participating NHS organisations would be induced to buy Allergan products, more or less to the exclusion of other glaucoma medicines. Further, the prescriber might be induced to prescribe only Allergan's products to new patients, and to switch patients who were on other products to an Allergan product. Alcon believed that this inducement would be achieved by way of changes to the formularies such that other manufacturers' products would be excluded or removed in favour of Allergan's products in order that PCTs maximised their rebate. Effectively, therefore, the scheme also induced PCTs to recommend Allergan products. Whilst the formulary would state in effect that the prescribing choice was ultimately subject to the health professional's discretion, the scheme would encourage the PCT to pressurise health professionals to prescribe Allergan's products as a first line treatment as a matter of course, thus ultimately infringing prescribers' rights to freely prescribe the medicine they considered most benefited the patient.

Clause 18.1

Alcon alleged that the scheme was in breach of Clause 18.1.

Alcon recognised that the scheme was not a conventional inducement to prescribe under Clause 18.1 because the inducement (the cash rebate) was not given directly to individual health professionals but rather to the NHS organisation. In this context, Alcon knew about the Code of Practice Appeal Board's ruling in Case AUTH/2095/2/08; Actelion v Encysive which Allergan had cited in inter-company dialogue.

However, Alcon did not believe that such a narrow construction should be given to Clause 18.1 considering that the scheme clearly did not comply with the principles of Clause 18, as revised in 2008. Indeed, Alcon noted that the scope of Clause 18 was significantly widened in 2008 when Clauses 18.5 and 18.6 were added, neither of which was limited to inducements to individual health professionals.

Alcon therefore understood that it was the clear intention of the 2008 Code to extend the restrictions on pharmaceutical companies in terms of offering inducements to prescribe, supply, administer, recommend, buy or sell any medicine in order to catch inducements in all contexts. Novel arrangements such as the one at issue - whereby a rebate was granted when a certain market share (expressed as a proportion of the total market) was attained - were perhaps not envisaged when Clause 18 was revised in 2008. Nevertheless, the scheme clearly violated the spirit of Clause 18. Alcon therefore maintained that the scheme breached Clause 18.1, as read in the light of Clauses 18.5 and 18.6.

Further, although the scheme did not allow direct payments to individual health professionals or to administrative staff, individuals might nonetheless benefit under the scheme because the rebate fund would be used at the discretion of the fund management executive.

Exemption to Clause 18.1

Allergan believed that the scheme was a legitimate form of volume based discount and that it therefore fell within the exemption to Clause 18.1. Whilst Allergan was correct that the offer of discounts on the supply of medicines was a well established and acceptable practice within the pharmaceutical industry, the scheme was evidently a novel form of discount arrangement because it was based on market share and thus depended on other products disappearing from the market. Allergan attempted to justify the fact that unit market share was the operative trigger for the rebate on the basis that this: '... enable[s] Primary Care Trusts and hospital trusts which serve the needs of smaller relevant patient populations to qualify for discounts even though the absolute volumes of glaucoma products prescribed for the patients for whom they are responsible may be smaller than some others'.

Allergan seemed to imply that structuring the scheme on the basis of unit market share targets was the only way that PCTs and hospital trusts which served the needs of smaller patient populations could benefit from a favourable price arrangement. However, such NHS organisations would alternatively benefit from a standard volume based discount (eg buy x amount and get y amount free), provided that x was based on a realistic purchasing target. Alcon's concern about the scheme was that the unit market share thresholds set would, *de facto*, compromise clinicians' freedom to prescribe the most appropriate product to patients and encourage irrational switching. Further, Alcon disagreed with Allergan's suggestion that the same risk of irrational prescribing might be said to arise with any volume discount arrangement. In contrast with the scheme, standard volume discount arrangements were not structured in such a way that there was the necessary effect of removing other products from the market. Moreover, the rebate did not provide a discount to the payer (the NHS) – rather, it was in the form of a fund which might be applied at the discretion of the fund managers. Alcon considered that the distinction between an arrangement which offered a discount to the payer and one which did not was an important one. This was illustrated in Case AUTH/691/4/98; Pasteur Mérieux MSD v Wyeth where Wyeth was ruled in breach of Clause 18.1 (as it then was) for offering practices which purchased its influenza vaccine a sum of money to be used for training. The Panel explained why there was a distinction between offering a standard discount vs a collateral benefit associated with the sale of medicines: 'The Panel accepted that observers might consider the position to be illogical in that the provision of a percentage of sales value in the form of a training grant was unacceptable under the Code whereas the allowance of an extra discount would not have been unacceptable. This was, however, the result of the exemption of discounts from the provisions relating to gifts, a situation which arose from the fact that the Code followed both UK and European law in this respect'. Although Clause 18 had since been revised, the case usefully illustrated why the arrangement at issue was not a standard volume based discount.

Alcon therefore disagreed with Allergan's assertion that the scheme was exempted from Clause 18.1 on the basis that it was a discount scheme. Indeed, the supplementary information to Clause 18.1 stated 'Measures or trade practices relating to prices, margins and discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993 are outside the scope of the Code...Other trade practices are subject to the Code'.

Allergan had provided no evidence that an arrangement such as the one at stake was in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993 and indeed, Alcon did not accept that this was the case. On the contrary, it should be noted that the Executive Summary attached to Allergan's agreement, stated in the first section that 'The Department of Health and ABPI changed the rules on the nature of commercial relationships between organisations of the NHS and the pharmaceutical industry in 2008 enabling new and innovative approaches to contracting with organisations of the NHS' [emphasis added].

Thus, Allergan itself characterised its scheme as a novel form of arrangement, which lent further support to Alcon's contention that such an arrangement was not in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993. For the sake of completeness, Alcon added that it appeared from the above statement as well as inter-company dialogue that Allergan believed that the scheme fell within legitimate joint working arrangements with the NHS. However, Alcon disputed this because one of the essential features of a joint working arrangement was that there was a pooling of resources, which the scheme lacked.

Accordingly, Alcon considered that the scheme was an inducement to prescribe Allergan's products in breach of Clause 18.1.

Clause 18.5

Alcon considered that there were two ways of looking at the scheme: either it was caught by Clause 18.1 or by Clause 18.5.

As explained above, the rebate did not provide a discount to the payer (ie, the NHS), which was a matter of concern to Alcon (and an indication that the rebate offered under the scheme was not a standard volume based discount), as explained above. Rather, the scheme provided a collateral benefit associated with the prescription of Allergan's glaucoma medicines (provided these met the requisite threshold) in the form of a cash fund that was apparently intended: '...to develop ophthalmic services in the community and or for the benefit of patients with ophthalmic conditions. However this is not an exclusive requirements - the fund management executive may decide to use the fund for purposes indirectly linked to ophthalmic patients or service development'.

Therefore, under Clause 18.5, the rebate might be seen as a kind of grant ostensibly intended for the provision of medical services. However, grants were only permitted under Clause 18.5 if they did not constitute an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. Alcon believed that the scheme induced the contracting NHS organisation to buy and recommend Allergan's glaucoma products, and the prescribers to prescribe them.

Alcon therefore alleged that the scheme was in breach of Clause 18.1, or in the alternative Clause 18.5. Alcon noted that the Authority's guidance on 'Joint working and the ABPI Code of Practice for the Pharmaceutical Industry' stated that although Clause 18.5 did not generally relate to activities involving the sale of medicines, it might apply 'if the company's medicines were not sold as part of the joint working'. As Alcon explained above, it believed that joint working had no application to the scheme and that Clause 18.5 was therefore relevant in this context.

Breach of Clause 7.2 – ability to form an opinion on the therapeutic value of the medicine

Alcon was concerned that the scheme was presented to NHS organisations in such a way that they were unable to form their own opinion of the therapeutic value of the medicine, irrespective of whether the arrangement was held to constitute an inducement for the purposes of Clause 18.

On the basis of inter-company correspondence as well as the slide presentation that Alcon understood Allergan used to promote the scheme, Alcon was not confident that NHS participating organisations were told that whilst increasing market share allowed hospitals to qualify for a cash rebate, additional costs would occur in the community where other glaucoma medicines offered cost effective alternatives (for example, compare Alcon's product Travatan at £10.17 vs Allergan's product Lumigan at £10.30).

Further, as a general point, Alcon considered that as a whole the scheme sought to distort the reality of the market (where there was an appropriate range of products to meet the individual needs of different patients), and incentivised NHS organisations to sign up to a scheme which imposed an unreasonable goal and which might not benefit the NHS in the long-run.

Alcon therefore considered that in seeking to attain the requisite thresholds for the grant of the rebate, NHS organisations might lose sight of the therapeutic value of Allergan's medicines such that they were prescribed irrationally, instead of as one possible product amongst an appropriate range of options.

Breach of Clause 9.1 – maintenance of high standards

Clause 9.1 provided that high standards must be maintained at all times.

Irrespective of whether the scheme was an inducement within the meaning of Clause 18, Alcon considered that it did not maintain high standards because it promoted Allergan's products at the expense of good medical practice (as explained above) and incentivised NHS organisations to get rid of other glaucoma medicines, which compromised the interests of patients.

Breach of Clause 2 – bringing discredit upon/reducing confidence in the pharmaceutical industry

Alcon noted that rulings of a breach of Clause 2 were reserved for cases of particular censure. It considered that this case warranted such censure and that irrespective of whether the scheme was an inducement to prescribe/recommend/buy Allergan's products (which Alcon strongly believed it was), it brought discredit upon, or at the very least reduced confidence in, the pharmaceutical industry. This was because Allergan effectively used the scheme to encourage NHS organisations to get rid of competing products, with the consequence that patients might not be prescribed the most appropriate product for them. The scheme was therefore detrimental to the interests of patients who would be victim to an unnecessary and inappropriate fettering of prescribers' discretion.

For the sake of completeness, Alcon did not believe that the application of Clause 2 was avoided on the basis that the stated intended purpose of the scheme was: '...to develop ophthalmic services in the community and or for the benefit of patients with ophthalmic conditions'. Whilst there might be

an overall benefit to ophthalmic patients as a general class, this might be at the expense of individuals who were denied the most appropriate product for their condition. Further, the scheme agreement specifically stated that: '... the fund management executive may decide to use the fund for purposes indirectly linked to ophthalmic patients or service development'. Therefore, it was certainly not guaranteed that there would be any benefit at all to ophthalmic patients, let alone the glaucoma patients who were directly affected by the scheme.

RESPONSE

By way of background Allergan provided copies of the scheme agreement, an executive summary, a powerpoint presentation and an internal briefing document. There were no other documents relating to the scheme. Allergan believed the scheme was a legitimate form of volume based discount and as such complied with Clause 18.1 of the Code and the UK Advertising Regulations. Allergan understood that the Authority accepted that discounts fell outside Regulation 21(1) of the Advertising Regulations because they were covered by the exemption in Regulation 21(4) and that such discounts might legitimately include financial rebates, providing these were transparently agreed and invoiced. A rebate was merely a financial term and a means of accounting for a quantity discount that was calculated over more than one account period and invoice.

The scheme was not a novel arrangement, it was a volume based discount, transparently agreed and invoiced. Therefore, the exemption provided by Clause 18.1 and Regulation 21(4) applied. The scheme and associated documentation was examined in this context, as a scheme that fell outside of the Code.

Overview of the scheme

The scheme was a commercial agreement relating to discounts through rebates between Allergan and either a national health trust, NHS health board or an NHS practice based commissioning organisation.

In outline, a retrospective rebate would be applied to the value of a range of Allergan ophthalmic medicines prescribed and dispensed within a defined geographic area for a defined period of time. The rebate would be paid on achievement of unit market share thresholds within the period of the agreement. The rebate was the percentage of the unit cash value (number of units of medicine prescribed multiplied by the NHS tariff price) at NHS tariff prices for the named Allergan glaucoma medicines issued to patients via a GP's prescription (FP10). Allergan products purchased by NHS secondary care trusts (from Allergan directly or via pharmaceutical wholesalers) were excluded from the agreement.

The use of unit (volume-based) market share thresholds as opposed to value based market share thresholds was important. Market share distorted the market position in Allergan's favour making its products appear to be more frequently used than they were, it measured relative value whereas unit share was absolute volume.

Unit share removed price from the equation giving all the products in the market a value of one. This meant that a doctor knew that a 17% unit share meant that 17 of every 100 patients were using that product. Market share measured the value of a market position in cash terms. Market share was the proportion in cash value of a given product in a market sector as measured by the cash worth of that market. This was a subtlety that distorted the market somewhat, as a lower volume product with a higher price would appear to most clinicians to be a relatively more frequent choice of product. As a simplistic example, if an established market comprised products at £2 per item and a new product entered the market at £20 per item then it would appear to be a popular choice in terms of market share because every one of the new medicines prescribed in market share terms was worth ten times the established market products.

Price	Volume	Value	Total Market	Unit Share	Market Share
£2	500	£1,000		83%	33%
£20	100	£2,000		17%	67%
			£3,000	100%	100%

Using unit share as the metric for the rebate scheme meant that when a doctor prescribed an Allergan product for a patient it counted as one, not as a proportion of the cash value of the market sector; it was easier for the clinician and authorities to understand and to keep in context. It also meant that all Allergan promoted glaucoma products counted equally. The importance of this was explained below.

The rebate was paid retrospectively as a cash fund into the business account of the NHS organization named in the agreement. The rebate was recorded through invoicing and was entirely transparent.

Before signing the agreement a fund management executive was appointed, typically three NHS employees, for example a pharmaceutical advisor, a medicines management or professional executive committee (PEC) lead, and an ophthalmologist or representative from the ophthalmic department.

Allergan broadly understood that the fund would be used to develop ophthalmic services in the community and/or for the benefit of patients with ophthalmic conditions. However, this was not a requirement – the fund management executive might decide to use the fund for purposes indirectly linked to ophthalmic patients or service development. The rebate fund would be used at the discretion of the fund management executive. Allergan had no influence over the use of the rebate fund. Indeed, the rebate could be put back into the

trust's medicine budget or paid into its capital expenditure account if so desired by the fund management executive.

Details of the scheme as requested by the Authority

Allergan submitted that the initial threshold was attainable for most areas which had its products on the formulary.

The Allergan noted its national unit share of its promoted portfolio in glaucoma. This was an average unit share, made up of the jigsaw of NHS organisations with differing influences and different decision makers. There was a normal distribution curve with outliers at either end. The majority of areas had a share close to the national and a significant volume of organizations were within 2% of the first threshold to trigger the scheme.

Currently, four areas had signed up to the scheme. Two entered with unit share above the first threshold, one with unit share above the second threshold and one was just below the first threshold. Approximately 36 others were considering the scheme and by the time they joined the scheme they would have achieved or be very close to the first threshold.

Overall, more than one in five NHS organisations had a unit share at or above the first threshold needed to trigger the scheme. However, there was massive variation in size between these organisations as it included the Scottish health boards and English PCTs.

Regarding the rebates paid to date, of the four areas currently signed up, three would be paid annually and one would be paid quarterly. Allergan had limited data, but the largest rebate, for the quarterly account, was projected to be no more than £1,200.

Regarding communication of the scheme to prescribers and NHS managers, as per the briefing document provided (UK/0046a/2008) the territory manager or area manager would contact the NHS business manager regarding a potential hospital that might be suitable for the scheme. The NHS manager would meet the lead clinician and PCT representative and present the scheme using the powerpoint presentation and document provided (UK/0046/2008). There was no additional documentation.

There was no communication with prescribers other than with those who formed part of the team assessing and, if appropriate, signing the agreement.

No Allergan employees were bonused according to take up of the scheme.

Response to specific allegations from Alcon

Alcon alleged that the scheme was a novel arrangement and operated as an inducement to prescribe, buy and recommend Allergan products. Allergan strongly disagreed.

Classification of the scheme as a standard volume based discount

As explained above, the rebate offered to NHS customers was calculated on the basis of unit market share. Customers, therefore, received a discount related to the volume of their orders; the higher the volume of orders the higher the discount. The total market share was relatively stable. In consequence, expressing the thresholds by reference to volume market shares was equivalent to expressing them in absolute volumes. Unit market share was chosen as the operative trigger to enable PCTs and hospital trusts, which served the needs of smaller relevant patient populations, to qualify for discounts even though the absolute volumes of products prescribed might be small. The scheme was, nevertheless, a volume based discount.

Allergan's experience of volume based discounts in the pharmaceutical industry was substantiated and pre-dated 1 January 1993. Allergan provided a list of such schemes as supporting evidence.

There was ample evidence of volume related retrospective rebate schemes in common use pre-1993, and in current practice from a number of named pharmaceutical companies. Indeed, Allergan understood that Alcon had recently offered volume related discounts to dispensing GPs and independent service providers. These agreements tended to be between pharmaceutical companies and dispensing GPs or pharmaceutical companies and NHS organisations such as buying groups or hospitals.

Allergan submitted that its scheme fell squarely within the parameters set out in the supplementary information to Clause 18.1 and the additional guidance provided by the MHRA in the Blue Guide 2005. It was a business to business discount scheme which was transparently agreed and invoiced and was of a type which was in regular use by a significant proportion of pharmaceutical industry before 1 January 1993. It was clear from the Blue Guide that, in order to benefit from the exemption, schemes did not have to be identical in every respect to schemes in use before 1993. The Blue Guide described by way of example of exempt schemes 'volume based discounts and similar offers' provided they were clearly identifiable and invoiced. Alcon's scheme did not, therefore, fall within the scope of the Advertising Regulations or the Code since there was nothing in the Code to suggest that the interpretation of exempt schemes should be narrower than that given in the Advertising Regulations. The Code required a higher burden of proof in that it required evidence that such schemes were in use by a significant proportion of the pharmaceutical industry before 1 January 1993, as opposed to merely being in existence before that date but Allergan considered

that this burden was fully discharged in any event by the examples given in the Blue Guide itself and as above.

As noted by Alcon, one bullet point in the general background document entitled 'Executive Summary for the Retrospective Rebate Initiative' mentioned changes in 2008 regarding joint working arrangements. However, Allergan submitted that it had never claimed its scheme was a joint working arrangement either to Alcon or with Allergan's customers. This bullet point was given for context alongside information on fast moving consumer goods/manufacturing industry retrospective discounts and general retrospective volume based discount schemes.

Clause 18

Even if the scheme was not exempt, there was no breach of Clause 18.1 as payments were made to institutions rather than to individuals. The Appeal Board ruling in Case AUTH/2095/2/08 was conclusive authority for this proposition. The 2008 amendments to the Code did not undermine the precedent set by this ruling.

Alcon had also alleged that the scheme breached Clause 18.5 which dealt with the provision of medical and educational goods and services in the form of donations, grants and benefits in kind. The scheme did not involve the provision of grants, donations or benefits in kind. It was a transparently agreed and invoiced business to business discount. Neither Directive 2001/83/EC, which was the legal basis for the 1994 Advertising Regulations, nor the Code was designed to prevent pharmaceutical companies competing for customers on price. Such a conclusion, which seemed to underlie Alcon's objections to the scheme, would be quite perverse and certainly illegal under European Community competition rules.

Clause 7.2

The alleged breach of Clause 7.2 was puzzling. Clinicians would have used a range of materials and documents to form their own opinion of the therapeutic value of a medicine. The hospital drugs and therapeutics committee would have decided to add the Allergan products to the formulary before any consideration of participating in the retrospective rebate scheme.

At a very basic level a prescriber would not use the retrospective rebate materials to help form their opinion regarding the therapeutic value of a medicine or medicines.

With regard to the rather tenuous allegation that an organisation (rather than an individual prescriber) would lose sight of the therapeutic value of Allergan's medicines, there was no evidence that any NHS organisation had been misled into joining the scheme against its better interests or those of its patients. Allergan took care that the documents setting up the scheme were signed by a person with authority to bind the contracting NHS organisation, with current signatories including a clinical director, director of pharmacy (x2) and a head of procurement. The fund into which the rebate was paid was administered by three senior appointees of the NHS organisation. Allergan had no influence on these appointments nor as to how the NHS organisation used the rebate.

It was simply not a feature of the scheme that it could lead to irrational prescribing. Doctors were required, by their professional code of ethics and, where they were GPs in contract with a PCT, by the terms of their contract, to take account of the best use of resources. This meant that where there was more than one equally suitable product the prescriber should prescribe the product which provided the best value. This did not necessarily mean the product which had the lowest acquisition cost. The value of rebates should also form part of that judgment. This much was evidenced by the numerous patient access schemes which had been approved by the Department of Health (DoH) in recent years and had been taken into account by NICE in its assessments of cost effectiveness.

The risk of 'irrational prescribing' (that might be said to arise with any volume discount arrangement) was not only avoided by the guidance to which Allergan had referred above, but also by the fact that the lowest rebate rate was 16% which meant, of course, that a rebate was due if 16 out of 100 patients got one of the three relevant Allergan products. None of those 16 Allergan products would be prescribed unless the prescriber considered that the product was suitable for the patient. The fact that another product might also be suitable but offered less value to the purchasing primary care organisation was quite properly a relevant factor to be taken into account by the prescriber in reaching his or her ultimate decision. The corollary was that 84 other patients could still be prescribed other products. The suggestion that such a scheme curtailed clinical freedom was without foundation and sat uncomfortably with the fact that hospitals awarded single product tenders that left prescribers with no choice at all, and yet, provided the NHS believed several different products met the same clinical need, this was not viewed as objectionable. Allergan did not consider it could be suggested that patient access schemes, to which its rebate scheme could be likened, were anything but beneficial to the NHS and to patients.

Clauses 9.1 and 2

Allergan submitted that the rebate scheme did not promote its glaucoma products at the expense of good medical practice. The interests of patients and participating NHS organisations were promoted by the scheme, in that glaucoma medicines, which prescribers had professionally judged suitable for their patients, were provided at excellent value. Such a scheme did not discredit or reduce confidence in the pharmaceutical industry. In

Allergan's view the scheme represented good practice in the pharmaceutical industry of a type which was encouraged by the DoH, NICE and by the ABPI itself, as evidenced by the terms of the 2009 Pharmaceutical Price Regulation Scheme.

Allergan noted that the pack of materials from the Authority included an Alcon briefing document entitled 'Allergan Rebate/Reimbursement Scheme'. Allergan believed it might have received this in error and noted that this document had not been part of this ongoing complaint, and that this was the first time it had seen this document. It contained unsubstantiated allegations and many inaccuracies about Allergan's scheme and its implementation. Allergan was concerned by the tone and content of this document and asked that it was not considered by the Authority as part of the complaint.

Competition law issues

As would be clear from the correspondence provided, far from being prejudiced by Allergan's reasonable refusal to disclose competitively-sensitive information to it, Alcon appeared to have had a copy of the scheme and supporting documentation since the start of inter-company dialogue. In response to Alcon's repeated requests for the disclosure of these competitively-sensitive documents, Allergan had always made clear that it was unwilling to disclose them because of its obligations under competition law. As the two companies were competitors, and given that the agreement contained competitively sensitive data concerning prices, Allergan had declined to share a copy of the scheme agreement. Allergan was concerned that Alcon had acquired this level of confidential and competitively-sensitive information.

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The Panel noted Allergan's request that the Alcon internal document entitled 'Allergan Rebate/Reimbursement Scheme' should not be considered by the Panel. That the document was not disclosed during inter-company dialogue would not prevent Alcon from submitting it to support the complaint. The document referred to matters which had been the subject of inter-company dialogue. It was for the Panel to decide what weight to attach to the document.

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PANEL RULING

The Panel noted that its concern was to consider the allegations in relation to the Code and not the MHRA Blue Guide or UK law.

The Panel noted that Allergan described the scheme as a commercial agreement relating to discounts through rebates between Allergan and either a national health trust, NHS health board or an NHS practice based commissioning organisation. The retrospective rebate scheme agreement set out the terms of the rebate agreement, the accumulation of the rebate community fund and the use of the fund. According to the agreement the rebate was paid on the achievement of unit market share thresholds within the period of the agreement (12 months) applied to the value of a range of prescribed and dispensed Allergan ophthalmic medicines. The rebate was paid as a cash fund retrospectively on a quarterly or annual basis into the NHS organisation's business account. Before signing the agreement a fund management executive was appointed comprising three NHS employees eg a pharmaceutical advisor, a medicines management or PEC lead and an ophthalmologist/representative from the ophthalmic department. The agreement stated that the fund was intended to be used to develop community ophthalmic services and/or for the benefit of patients with ophthalmic conditions. However this was not an exclusive requirement – the fund management executive could decide to use the fund for purposes indirectly linked to ophthalmic patients or service development. Allergan would not influence or attempt to influence the use of the rebate fund. The agreement could only be cancelled early by mutual consent.

An executive summary set out the background to rebate schemes noting that the DoH and the ABPI changed the rules on the nature of commercial relationships between NHS organisations and the pharmaceutical industry in 2008 enabling new and innovative approaches to contracting. It stated that the rebate fund provided much needed cash liquidity to organisations rich in notional cash such as prescribing budgets. The executive summary differed from the agreement in its description of the governance of the rebate funding; it stated that no payments could be made to individuals other than cash payments to certain individuals through the NHS payroll. The agreement however was silent on this point.

The powerpoint presentation 'B2B [business to business] Retrospective Discount Scheme' stated that to work within the Code the accrued cash fund would be treated as a separate trust-fund administered by a committee of stakeholders to manage and agree on the use of the fund which would be available to purchase products and services which would be recorded for audit. The Panel noted that the presentation was not wholly consistent with the agreement on this point.

The Panel noted that Clause 1.2 excluded from the definition of promotion measures or trade practices relating to prices, margins or discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993. Further the supplementary information to Clause 18.1 stated that such measures or trade practices were excluded from the provision of that clause. Other trade practices were subject to the Code. The terms prices, margins and discounts were primarily financial terms.

The Panel noted that Allergan had provided brief details of schemes run by six companies which it argued either previously or currently provided volume based discounts to dispensing GPs and others. The Panel considered, however, that there was an important difference between a cash rebate and a discount. Only two of the schemes detailed by Allergan referred to rebates; the precise details of the schemes were unknown. The Panel noted that the Allergan scheme linked primary care prescribing volumes to a product where prescribing was usually initiated in secondary care. The agreement at issue covered both the cash rebate and the administration of the subsequent trust fund. The Panel considered that the establishment of a managed trust fund wherein cash accumulated was an integral part of the retrospective rebate scheme. Allergan had provided no evidence that such composite schemes were in regular use by the pharmaceutical industry prior to 1 January 1993. The Panel considered that such composite schemes could not take the benefit of the exemption. The scheme was thus subject to the Code.

The Panel noted that the agreement set out a loose framework for the establishment and operation of the rebate fund. According to the agreement Allergan would not influence or attempt to influence the use of the fund nor was it represented on the fund management executive. Fund managers would be given a monthly statement on the fund accrual. Monies would be paid quarterly or annually.

The Panel noted Alcon's allegation that the scheme operated as an inducement to prescribe Allergan's products contrary to Clause 18.1. From the market details provided by Allergan the Panel assumed that many areas would have to increase their prescribing of Allergan's products in order to reach the first threshold and thus qualify for a rebate. Four areas had signed up to the scheme of which two had unit shares above the first threshold, one above the second threshold and the other just below the first threshold. The Panel considered that insofar as the scheme encouraged the trust to persuade prescribers to increase their prescribing so that the trust could gain a cash rebate, or increase its cash rebate, it could be interpreted as an inducement. The Panel noted that Clause 18.1 related to inducements to individuals rather than organisations. The Panel considered that the scheme did not operate as an inducement to individuals nor was there evidence that payments had been made from a rebate fund to individuals as an inducement to prescribe or recommend Allergan's medicines contrary to the provisions of Clause 18.1. No breach of that clause was ruled

The Panel noted the intended purpose of the rebate fund as set out in the Retrospective Rebate Scheme Agreement, namely to directly or indirectly develop ophthalmic services in the community and/or for the benefit of patients with ophthalmic conditions. The Panel considered that the rebate scheme in effect could be seen as a donation, grant or benefit in kind and should thus comply with Clause 18.5.

The Panel noted that in the representatives' briefing document in a section entitled 'Actions to get started', step one involved the identification of hospitals with a market share above a stated percentage. The formulary status of all three glaucoma products in the hospital had to be determined and if one or more were not in the formulary immediate action was to be taken to gain formulary listings and also a special prices offer to the hospital pharmacy for all three glaucoma products must be made. Further, once the agreement had been signed the territory manager would support participating units with appropriate educational events and meetings. It thus appeared that a package of support was provided to the NHS organisation in addition to the cash rebate. The Panel considered that the provision of the cash rebate as a donation, grant or benefit in kind to the NHS organisation was inextricably linked to the promotion of Allergan's glaucoma medicines such that it amounted to an inducement to prescribe, supply, administer, recommend or buy such medicines contrary to Clause 18.5. A breach of that clause was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel did not consider that the scheme was such that it made claims about the therapeutic value of Allergan's medicines. In that regard the scheme was not such that it would prevent prescribers from forming their own opinion of the therapeutic value of the medicines. No breach of Clause 7.2 was ruled.

The Panel was concerned that the arrangements were such as to bring discredit upon or reduce confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

APPEAL BY ALLERGAN

Allergan stated that the following were the essential elements for the retrospective rebate scheme:

- The scheme related to the sales of Allergan's products for glaucoma. There was a range of products available to ophthalmologists with which to treat their glaucoma patients. Allergan had a minor share in this market. In many cases, several products, including, Allergan's, would be equally suitable for treating a particular patient.
- The prescription of products for glaucoma was initiated by ophthalmic specialists in secondary care. Repeat prescriptions were often provided in primary care but there was little or no opportunity for a GP to initiate or change a patient's medicine, as he or she was seldom qualified to make that decision.
- Ophthalmic services in primary care were commissioned by primary care trusts and commissioning organisations, who were active participants in the design of those services.
- The scheme was promoted to primary care trusts, hospital trusts, NHS practice based commissioning organisations and NHS health boards. It was not promoted to individual prescribers.

- The scheme offered a cash rebate to participating organisations payable if FP10 prescriptions of Allergan's glaucoma products in a relevant geographical primary care area exceeded certain volume based thresholds. The maximum cash rebate rate was capped at a set percentage.
- The thresholds were expressed as a percentage of unit (rather than value) market share in order not to discriminate against organisations serving small geographical areas or ones with a sparse population.
- The first threshold was set to reflect the range of existing observed prescribing levels across a range of trusts.
- No NHS organisation was required to agree to prescribe Allergan's products in order to take part in the scheme. Allergan's products needed only to be available as an option for ophthalmic specialists to prescribe if they judged them to be suitable for any particular patient.
- Any NHS organisation wishing to take part in the scheme had to sign an agreement in which the arrangements for the cash rebate were described. The signatory was in all cases a senior manager with authority to enter into agreements on behalf of the trust.
- The fund into which the cash rebate was paid was maintained in the business account of the participating NHS organisation and administered by three senior employees, for example, a pharmaceutical adviser, an ophthalmologist, a medicines manager or, in the case of primary care organisations, a professional executive committee lead.
- The fund administrators decided how to use the rebate.
- Allergan had no influence and, in most cases, no knowledge of how the funds were used. The funds would in all cases benefit the NHS, however, in the absence of undetected fraud by the fund administrators. There was no suggestion in the complaint or in the ruling that the funds had been used for anything other than the benefit of NHS patients.
- NHS organisations signing up to the scheme might be additionally offered educational activities but the provision of these services was not linked to any level of prescriptions for Allergan products or any prescriptions at all. The provision of educational services was not linked to any claim for a rebate on purchases.

Allergan submitted that the scheme was exempt from the scope of the Code and that, even if it was not found to be exempt from the scope of the Code, it did not breach Clause 18.5. The retrospective rebate scheme was an example of a measure or trade practice relating to prices, margins and discounts in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993. Such activities were outside the scope of the Code, as provided for in Clause 1.2.

Allergan submitted that this exclusion derived from that fact that the provisions of the Code to a significant extent reflected the legal framework regulating pharmaceutical advertising provided for by Article VIIIa of Directive 2001/83/EC (the 'Directive'). Recital (50) to the Directive provided that 'persons qualified to prescribe medicinal products must be able to carry out these functions objectively without being influenced by direct or indirect financial inducements'. This aim found legislative form in Article 94 of the Directive which prohibited the offer of '... gifts, pecuniary advantages or benefits in kind to persons qualified to prescribe or supply them unless they are inexpensive and relevant to the practice of medicine or pharmacy' whilst providing that 'Existing measures or trade practices in Member States relating to prices, margins and discounts shall not be affected ...'.

Allergan submitted that the provisions of Article 94 were transposed into English law by the Medicines (Advertising) Regulations 1994. Regulation 21 reproduced the prohibition on inducements to persons qualified to prescribe or supply medicinal products and the exemption for trade practices, dating the exemption from 1 January 1993, the date when the Directive came into force.

Allergan submitted that whilst the Panel's function was to deal with the Code and not the law, the provisions of the Code must be set in a proper context. The UK, as a Member State of the EU, had an obligation pursuant to the Treaty on the Functioning of the European Union (often referred to as the Lisbon Treaty) to ensure that the objectives of the Directive were attained. Article 97 allowed for self regulation and, therefore, pursuant to the Memorandum of Understanding made between the ABPI, the PMCPA and the MHRA, the MHRA did not intervene in self regulatory decisions made by the PMCPA except in rare circumstances.

Allergan submitted that it would be an unusual state of affairs if the Code purported to regulate aspects of the promotion of medicines which were expressly excluded from the European framework and its transposition into English law. Since the provisions of Title VIIIa of the Directive had been held by the Court of Justice in Luxembourg to be measures requiring complete harmonisation, Member States must ensure that the relevant local rules did not go beyond what was required by the Directive. It followed that in agreeing to self regulation by the PMCPA, the MHRA must have intended such self regulation to encompass those areas of pharmaceutical advertising dealt with by the Directive. The Directive expressly excluded existing 'trade practices, margins and discounts' from the scope of the prohibition on inducements to persons qualified to prescribe or supply them. Allergan submitted in order to give effect to the harmonizing aim of the Directive it was necessary to interpret the scope of this exemption in the same way throughout the EU, whether it was transposed into law or applied in a self regulatory context. This was not a case where the Code could properly provide definition to a principle contained in the law eg the meaning of 'inexpensive gift'.

Allergan, therefore, submitted that the Panel was wrong to suggest that the MHRA 'Blue Guide' had no relevance to its interpretation of the exemption from the scope of the Code provided for in Clause 1.2. The Blue Guide interpreted the exemption from the prohibition thus 'These are primarily financial terms and normally cover cash discounts or equivalent business discount schemes on purchases of medicinal products, including volume discounts and similar offers such as "14 for the price of 12", provided they are clearly identifiable and invoiced.' Allergan's retrospective rebate scheme was a variety of volume discount scheme, as described above, and was clearly identifiable and invoiced. The Blue Guide made it clear that exempt trade practices did not have to be identical in every respect to schemes in existence on 1 January 1993 but might be 'similar'. Allergan's scheme was similar to volume discount schemes which it had demonstrated were in use before January 1993 and which corresponded to the MHRA's description of exempt schemes. The Panel found that there was an important difference between a rebate scheme and a discount. Allergan submitted that this was not a well founded distinction. All that Allergan's scheme did was to give money back to the NHS if it bought more than a certain number of products. It gave cash back after the purchase of a number of products as opposed to a lower price on the purchase of a number of products. The purchaser, in this case the NHS, had money refunded retrospectively rather than building the same amount up by way of savings prospectively, as would be the case with a discount. The ultimate result was the same. The NHS had more money to spend on its own priorities. In a market where there was no or low growth, such as glaucoma, a volume based discount had the same effect as a volume based rebate. In both cases, a growth in demand for Allergan's products inevitably lead to a decline in the demand for others. If a volume based discount was permissible, there was no reason to treat a rebate scheme any differently. Unless all the product required by a trust were to be supplied under one, yearly invoice, which was most unlikely, a volume discount necessarily would have to be calculated retrospectively. Allergan was aware that the MHRA did not treat rebates and discounts differently in relation to the Advertising Regulations, so long as they were transparently invoiced and accounted for.

Allergan submitted that the scheme should, therefore, be exempt from the scope of the Code and was an entirely commonplace commercial practice which provided a commercial benefit for it and the NHS. Neither European law nor UK law was intended to outlaw such practices, even where they applied to commercial dealings between persons qualified to prescribe or supply and sellers of pharmaceutical products. Where, as in the case of Allergan's scheme, the arrangement was a business to business dealing which did not purport to offer any financial benefit to individual prescribers the argument could be made with even greater force that it fell completely outside the permitted scope of the regulation of pharmaceutical advertising in the EU, whether by law or by a self regulatory body. Allergan noted that the Panel had ruled no breach of Clause 18.1 ie that the scheme did not offer individuals financial inducements.

The Panel appeared to find that because the scheme offered a rebate for prescribing in primary care where the prescription was initiated in secondary care it was a composite scheme which could not take the benefit of the exemption. Allergan had noted that, in effect, GPs merely prescribed the product chosen by the specialist ophthalmologist to whom they had referred their patient. Ophthalmological services in secondary care were largely commissioned by primary care organisations. Services would not be commissioned if they did not provide value to both parties. The fact that that NHS purchasing and commissioning structures had been reformed since 1993 should be immaterial to the Appeal Board's deliberations.

Allergan submitted that its scheme allowed the NHS to gain additional value in the purchase of its medicines and did not financially reward any individual. Pharmaceutical companies had offered such schemes, different in detail but identical in aim, since the inception of the NHS and continued to do so. The recent interest in patient access schemes to provide access to medicines that would otherwise be deemed by NICE too expensive for the NHS to buy, illustrated this well. A number of such schemes offered rebates, some offered discounts and others offered free products. Most based the receipt of these financial benefits on demonstrations of efficacy, in individual patients or more generally in the longer term. Innovative flexible pricing schemes were expressly encouraged by the DoH and the ABPI by the terms of the 2009 PPRS. No schemes identical in detail to these schemes were known in 1993. On the principles applied by the Panel in its ruling that Allergan's scheme breached the Code, all such schemes would also constitute such breaches. Allergan submitted that this could not be the right conclusion. A proper interpretation of the Code would exclude from its scope all such business to business schemes which did not induce individuals to prescribe.

In the event that the Appeal Board did not agree with Allergan's submission that its scheme was exempt from the scope of the Code, Allergan submitted that the retrospective rebate scheme did not breach Clause 18.5 of the Code. Clause 18.5 was added to the 2008 Code of Practice, together with Clause 18.6, ostensibly to comply with amendments to the EFPIA (European Federation of Pharmaceutical Industries and Associations) Code. There was nothing in the public pronouncements on the changes to the Code made in 2008 to suggest that it created an entirely new obligation on ABPI member companies or others who were subject to the Code. On its face it appeared to be a restatement and clarification of Clause 18.4 which provided that medical and educational goods and services might be provided subject to the provisions

of Clause 18.1 if they enhanced patient care or benefitted the NHS and enhanced [sic] patient care. Allergan submitted that its scheme clearly did not breach Clause 18.4 and no complaint had been made that it did. There was no provision of goods or services pursuant to the scheme and no provision of inducements to individuals contrary to Clause 18.1. Clause 18.5 provided that 'The provision of medical and educational goods and services in the form of donations, grants and benefits in kind to institutions, organisations or associations that are comprised of health professionals and/or that provide healthcare or conduct research (that are not otherwise covered by the Code) are only allowed if;

- they comply with Clause 18.4 or are made for the purposes of supporting research
- they are documented and kept on record by the company
- they do not constitute an inducement to prescribe, supply, administer, recommend, buy or sell any medicine'.

If the Appeal Board found that Allergan's retrospective discount scheme was subject to the Code then Allergan submitted that the circumstances of the scheme did not disclose a breach of Clause 18.5. The cash rebate paid into the NHS organisation's business account was not a grant or a donation in the nature of a provision of goods or services of a medical or educational nature; it was a commercial rebate. A grant or donation implied that money was given without condition and not in exchange for something. It was simply a gift. Allergan's cash rebate was a business arrangement whereby the rebate was given in exchange for a particular number of purchases. It is not a donation or grant or a gift and was not treated in Allergan's accounts as such. It was a rebate on the sale price of the products in question.

Allergan submitted that the Panel's ruling of a breach of Clause of 18.5 was predicated on its conclusion, which did not appear to be based on any preceding reasoning or evidence, that the rebate scheme in effect could be seen as donation, grant or benefit in kind. In common parlance as well as in law a donation was distinguishable from a contractual payment in that it was not made consequent upon any agreement imposing an obligation that it should be paid or on a right to receive it. A donation was a gift; a cash rebate was not a gift. A cash rebate became due if the terms of a pre-existing contract gave rise to an obligation requiring its payment by one party to the other. Allergan had entered into an agreement with NHS organisations that the rebate would be paid if certain target sales volumes were reached. This was a contractual payment and not a donation. It was not prohibited by Clause 18.5. This analysis was supported by advice published by the PMCPA on its website commenting on joint working arrangements between the pharmaceutical industry and the NHS. The Allergan scheme was clearly not a joint working arrangement as it did not meet the required criteria laid out in the ABPI Guidance Notes on Joint Working between Pharmaceutical Companies and the NHS and Others for the Benefit of Patients (March 2009). However, the PMCPA advice provided additional interpretation of Clauses 18.5 and 18.6 and was not confined to their application to joint working arrangements. The advice stated:

> 'Clause 18.5 relates to donations and grants etc and not to activities involving the sale of medicines.
>
> It seems that Clause 18.5 would have no application to arrangements where goods and/or services are provided as part of an agreement between an institution and a company which involves the sale of medicines by the company to the institution.'

Allergan submitted that this advice was correct and meant that Allergan's retrospective rebate scheme, which was an arrangement involving the sale of medicines by the company to the institution, could not give rise to a breach of Clause 18.5. Allergan submitted that the proper interpretation of Clause 18.5 was that grants and donations to organisations which provided healthcare must benefit the NHS and must not constitute an inducement by way of a gift, benefit in kind or pecuniary advantage to a the health professional. It would then represent a helpful clarification of, and be entirely consistent with, both Clauses 18.1 and 18.4, and would prohibit donations to organisations which, in fact, turned out to provide a benefit to individual health professionals. It was not intended to prevent business rebates and the concern that this should be clear was evident from the PMCPA's advice which was particularly directed to ensure that innovative funding arrangements, such as the scheme at issue which provided value to the NHS were not outlawed by the Code.

If the Appeal Board found that there had been no breach of Clause 18.5 then the findings of breaches of Clauses 9.1 and Clause 2 fell away. In the event that the Appeal Board ruled a breach of Clause 18.5 then Allergan submitted that any such breach was not so severe as to warrant a finding that high standards had not been maintained or that confidence in the pharmaceutical industry had been reduced. The scheme was totally transparent and formed the basis of a commercial contract between an NHS organisation and Allergan. These arrangements would have been reviewed and approved at a senior management level at each participating trust. There had been no complaints from any of the trusts. The scheme fell squarely within the type of schemes permitted by the document published by the DoH in 2000 entitled 'Commercial sponsorship - ethical standards for the NHS' which stated:

> 'PCGs, health authorities and primary care contractors will need to consider issues such as:
> ....
>
> Purchasing decision, including those concerning pharmaceutical and appliances, should always be taken on the basis of best clinical practice and

value for money. Such decisions should take into account their impact on other parts of the health care system, for example, products dispensed in hospital which are likely to be required regularly by patients at home.

Hospital trusts who are offered significant discounts on drugs may wish to consult the relevant PCG/PCT about possible implications for subsequent prescribing in primary care.'

An example was given of a situation where a manufacturer of a particular type of nicotine replacement therapy offered to provide its product at a reduced rate to a Health Action Zone or a health authority. It was stated that 'This arrangement is acceptable provided that there is a clear clinical view that these products are appropriate to particular patients and there is no obligation to also prescribe these products to other patients for whom an alternative product would be equally beneficial'.

Allergan submitted that its scheme did not require any of its products to be prescribed. The rebate was only paid if sufficient numbers of products were prescribed, but there was no obligation to prescribe them. The decision rested with the individual clinician. If Allergan's scheme met the ethical standards of the NHS set by the DoH, participating trusts being well aware of their responsibility to liaise with primary care prescribing, Allergan submitted that the scheme could not be judged to have failed to maintain high standards or brought discredit on the pharmaceutical industry.

COMMENTS FROM ALCON

Alcon alleged that under the scheme, NHS organisations were granted a retrospective cash rebate which was to be held in a trust fund for the provision of ophthalmic services, together with a package of support, provided that prescriptions of Allergan's products reached a certain unit market share threshold within a particular geographical area. The majority of NHS organisations would not be entitled to any retrospective rebate (let alone the highest level of rebate), unless they displaced competitor products (by the questionable approach of switching patients unnecessarily who were currently well controlled on a non-Allergan product to an Allergan-product). In promoting the scheme, Allergan had not maintained high standards and its activity brought discredit upon or, at the very least, reduced confidence in the pharmaceutical industry.

Alcon noted that in its response, Allergan had set out what it considered to be the essential elements of the scheme. However, rather than presenting an objective summary of the facts, Allergan had made several disingenuous remarks which warranted comment as explained below (for ease Alcon had followed the order of Allergan's bullet points).

- In the 1st bullet, Allergan characterised its share in the glaucoma market as minor.

Alcon alleged that in this context, it should be noted that entitlement to the retrospective rebate depended on the NHS organisation attaining a significant to major share of the market. As Allergan acknowledged, the glaucoma market was subject to slow growth with very few new entrants, which meant that the only means of securing a greater market share was to decrease the share held by competing products. Consequently, patients must be switched from a non-Allergan product to an Allergan product in order to reach the required threshold to obtain the retrospective rebate.

- In the 2nd bullet, Allergan explained that the prescription of glaucoma products was initiated by ophthalmic specialists in secondary care and that whilst repeat prescriptions were often provided in primary care, there was little or no opportunity for a GP to initiate or change a patient's medication, as he or she would seldom be required to make that decision.

Alcon alleged that Allergan appeared to suggest that in so far as the scheme was promoted to PCTs, it would not trigger an increase in prescriptions of Allergan's products. However, it was clear from Allergan's briefing document for representatives that its strategy in relation to primary care was to target those organisations which had the capacity to influence prescribing. Indeed, it was stated under the heading 'Step two (primary care)' in the action list: 'Capability of commissioned organization to influence prescribing is assessed' which could imply that if they were not capable of influencing prescribing then they should not be involved. This document set out instructions for representatives in the form of 'Actions to get started'; step two had two limbs – an approach for hospitals and an approach for primary care.

Alcon further alleged that GPs were expected to follow the PCT or practice guidance (or formulary where available) with regards to prescribing. Although the choice of what to prescribe was ultimately at the clinical discretion of the GP, GPs would know that the PCT might not increase the practice's annual medicine budget if the practice ran up a significant medicine bill (and this was seen to be a consequence of the under-prescribing of medicines listed in the formulary or guidance). It appeared that Allergan was specifically targeting those primary care organisations which would be effective in influencing prescribing, GPs would face pressure to switch patients from a non-Allergan product to an Allergan product in order to achieve the unit market share threshold.

- In the 6th bullet, Allergan stated that the retrospective rebate thresholds were expressed as a percentage of unit (rather than value) market share in order not to discriminate against organisations serving small geographical areas or with a sparse population.

Alcon alleged that Allergan seemed to imply that structuring the scheme on the basis of unit market

share targets was the only way that PCTs and hospital trusts which served the needs of small patient populations could benefit from a favourable price agreement. However, a pricing agreement did not have to (and should not) be structured such that its success depended on displacing competitors' products. Indeed such NHS organisations could alternatively benefit from a standard volume based discount which would not operate as an inducement (eg 'buy x amount and get y amount free'), provided that 'x' was actually based on a realistic purchasing target.

Alcon alleged that further, it appeared that the unit market share thresholds under the scheme were not adjusted as between different geographical areas in order to take account of the 'natural' market conditions (ie in the absence of the scheme). This meant that NHS organisations in some geographical areas would have to significantly increase prescribing levels for Allergan products in order to meet even the lowest unit market share threshold.

- In the 7th bullet, Allergan stated that the lowest market share threshold was set to reflect the range of existing observed prescribing levels across a range of trusts.

Alcon alleged that notably, Allergan did not comment on the higher market share thresholds which did not generally reflect existing observed prescribing levels. Clearly, NHS organisations participating in the scheme would want to meet the highest threshold in order to benefit from a major financial retrospective rebate at the end of the accounting period.

- In the 8th bullet, Allergan asserted that no NHS organisation was required to agree to prescribe Allergan's products in order to take part in the scheme. Allergan's products needed only to be available as an option for ophthalmic specialists to prescribe if it judged them to be suitable for any particular patient. Alcon alleged that this statement was misleading. The relevant point was that an NHS organisation was required to attain a certain level of prescriptions (calculated as market share) in order to derive the real benefit from the scheme (namely, the retrospective rebate). *De facto*, NHS organisations were required to prescribe Allergan products (or recommend these products for prescription). Further, and as explained below in relation to the final bullet, the provision of educational services was linked to the prescription of Allergan products.

- In the 12th bullet, Allergan stated that it had no influence and, in most cases, no knowledge of the way in which the funds were used. Nevertheless, it should be noted that the scheme provided a collateral benefit for participating NHS organisations, namely the means '... to develop ophthalmic services in the community and or for the benefit of patients with ophthalmic conditions' as stated in the agreement by way of a trust fund. The composite nature of the scheme (retrospective cash rebate plus administration of trust fund) was a factor of relevance in the Panel's ruling on Clause 18.5.

- In the 13th bullet, Allergan claimed that the provision of educational services to NHS organisations signing up to the scheme was not linked to any level of prescriptions for its products or any prescriptions at all. The provision of educational services was not linked to any claim for a rebate on purchases. Alcon alleged that clearly, however, the provision of educational services was *de facto* linked to prescriptions for Allergan products and a retrospective rebate on purchases. The objective of the scheme was to increase prescriptions for Allergan products; the educational services were provided to facilitate this objective (indeed, such services were provided to participating units, as stated in Allergan's 'Retrospective Rebate Initiative – Briefing Document for Representatives', under 'Step four').

Why the scheme was not exempt from the Code

Alcon alleged that the primary basis for Allergan's appeal was that the scheme fell outside the scope of the Code because it was an example of a measure or trade practice relating to prices, margins and discounts in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993 (and was therefore exempt under Clause 1.2). Further, Allergan argued that this exemption should be understood within the context of the prohibition on inducements to individual persons qualified to prescribe in accordance with Article 94 of Directive 2001/83/EC (as amended) (the 'Directive'), as transposed into English law by Regulation 21 of the Medicines (Advertising) Regulations 1994 (the 'Regulations'). Thus, Allergan argued that:

- the scheme was not subject to the Code on the basis that it benefitted from the Clause 1.2 exemption; and
- in any event, it did not breach Clause 18.5 because the retrospective rebate was not a donation or grant within the meaning of Clause 18.5 and, further, that clause prohibited only financial inducements to individual members of the health profession.

Alcon alleged that in support of its argument, Allergan resorted to challenging the very nature of self regulation. Allergan commented that it would be an unusual state of affairs if the Code purported to regulate aspects of the promotion of medicinal products which were expressly excluded from the European framework and its transposition into English law. However, the aspects of the Code to which Allergan referred did not purport to regulate aspects of the promotion of medicinal products which were 'expressly excluded' from the European legal framework (which had been transposed into English law). This was explained below in relation

to a) the scope of the Clause 1.2 exemption; and b) the scope of the Clause 18.5 prohibition.

The scope of the Clause 1.2 exemption

Alcon noted that the Code excluded from its scope 'measures or trade practices relating to prices, margins or discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993'. This was a general exemption and, if applicable in the present case (which Alcon refuted), would take Allergan's scheme outside the scope of the Code entirely. Article 94(4) of the Directive provided a similar exemption in the context of the provision regarding inducements (for ease of reference, Article 94 was set out in full below):

1. 'Where medicinal products are being promoted to persons qualified to prescribe or supply them, no gifts, pecuniary advantages or benefits in kind may be supplied, offered or promised to such persons unless they are inexpensive and relevant to the practice of medicine or pharmacy.
2. Hospitality at sales promotion events shall always be strictly limited to their main purpose and must not be extended to persons other than healthcare professionals.
3. Persons qualified to prescribe or supply medicinal products shall not solicit or accept any inducement prohibited under paragraph 1 or contrary to paragraph 2.
4. **Existing measures or trade practices in Member States relating to prices, margins and discounts shall not be affected by paragraphs 1, 2 and 3'** (emphasis added).

Article 94 has been transposed into English law by Regulation 21 of the Advertising Regulations; Regulation 21(4) provided that 'Nothing in this regulation shall affect measures or trade practices relating to prices, margins or discounts which were in existence on 1st January 1993'.

Alcon alleged that it was clear from the above that the Code's Clause 1.2 exemption was narrower than the Article 94(4)/Regulation 21(4) exemption: whereas the Code provided that only those measures and trade practices 'in **regular** use by a **significant proportion** of the pharmaceutical industry on 1 January 1993' (emphasis added) were exempt, the Directive and Regulations excluded from their scope all measures and trade practices which were merely 'in existence' on 1 January 1993. The Directive was a consolidation of various previous Directives, including Council Directive 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use which came into force on 1 January 1993. This was why 'existing' (ie existing as at 1 January 1993) measures or trade practices in Member States relating to prices, margins and discounts were excluded from the prohibition on inducements. Clearly, the scheme was novel (and was not in existence – let alone in regular use - as at 1 January 1993); indeed, it was acknowledged by Allergan to be 'innovative' in the Executive Summary to the Scheme Agreement (as explained in Alcon's complaint). The factors which the Panel took into account in deciding that the scheme did not benefit from the Clause 1.2 exemption (namely, the scheme's composite nature, and the fact that many NHS organisations would have to increase their prescribing to benefit from the retrospective rebate) were discussed further below.

Further, contrary to Allergan's suggestion, Alcon alleged that this did not mean that the Code was regulating aspects of the promotion of medicinal products expressly excluded by the EU legal framework. Firstly, it had already been explained above that the scheme did not benefit from the exemption in the Directive/Regulation, or in the Code. Secondly, it had been clearly established that the Code extended beyond UK legal requirements (implementing the Directive), which was entirely legitimate (contrary to what Allergan argued). Indeed, Article 97(5) of the Directive stated that the provisions regarding the monitoring, vetting and legal action that might be taken in relation to advertising '... shall not exclude the voluntary control of advertising of medicinal products by self-regulatory bodies and recourse to such bodies, if proceedings before such bodies are possible in addition to the judicial or administrative proceedings referred to in paragraph 1'. Accordingly, the Directive specifically did not exclude the self-regulation of advertising and, moreover, did not limit the scope of self-regulation. Indeed, as stated on the PMCPA's website 'In addition to the Code, there is extensive UK and European law relating to the promotion of medicines. The Code **reflects and extends beyond the legal requirements** controlling the advertising of medicines' (emphasis added). Further, the Memorandum of Understanding between the ABPI, PMCPA and MHRA specifically acknowledged that: 'The ABPI Code covers and extends beyond UK law and it is thus possible that material pre-vetted and approved by the MHRA might subsequently be ruled in breach of the ABPI Code'.

For this reason, the Memorandum of Understanding established that: 'The MHRA will also refer complaints about relevant matters not covered by UK law to the PMCPA for consideration under the ABPI Code'.

Alcon alleged that clearly, therefore, the purpose of the Code was not limited to providing detail on principles enshrined in the legislation as Allergan claimed; rather, the scope of the Code extended beyond the law, which was why material which did not fall foul of the UK law (and the MHRA's Blue Guide) might nevertheless be found in breach of the Code. Accordingly, the Panel applied the correct standard in assessing whether Allergan's Scheme was of a type in regular use by the pharmaceutical industry. The reason why the PMCPA did not accept that the Scheme benefitted from the Clause 1.2 exemption was its composite nature (namely, retrospective cash rebate plus administration of subsequent trust fund): 'Allergan had provided no

evidence that such composite schemes were in regular use by the pharmaceutical industry prior to 1 January 1993. The Panel considered that such composite schemes could not take the benefit of the exemption. The scheme was thus subject to the Code'.

Alcon noted that Allergan had stated that the Panel appeared to find that the fact that the scheme offered a rebate for prescribing in primary care where the prescription was initiated in secondary care rendered it a composite scheme which could not take the benefit of the exemption. In this regard Allergan appeared to have misunderstood the Panel's ruling; the scheme was composite because it consisted of a retrospective rebate plus administration of a trust fund. The fact that the scheme linked primary care prescribing volumes to products where prescribing was usually initiated in secondary care was however relevant to the Panel's finding that the arrangement was inappropriate (the scheme sought to influence primary care prescribing patterns).

The Panel also noted that there was an important difference between a cash rebate and a discount. Allergan disputed this distinction, and argued that the ultimate result was the same. The NHS had more money to spend on its own priorities. Allergan submitted that in a market where there was no or low growth, such as glaucoma, a volume based discount had precisely the same effect as a volume based rebate. In both cases, a growth in demand for Allergan's products inevitably led to a decline in the demand for others. Alcon alleged that Allergan's statement was misleading because it oversimplified the circumstances at stake. The present case was not straightforward: the retrospective rebate did not operate like an 'inverse' discount - in other words, the issue was not whether, for example, '14 for the price of 12' (standard discount) was different in principle from 'Buy 14 and get a refund for 2' (standard retrospective rebate). The important difference identified by the Panel between Allergan's retrospective cash rebate and a standard discount was that, as explained above, the scheme was composite – which meant that it did not provide cash to the payer (the NHS) as a standard discount (or even a standard rebate) would. Rather, the retrospective rebate took the form of a fund which might be applied at the discretion of the fund managers (which was also relevant to the breach of Clause 18.5, as explained below). It was noted that the Panel distinguished the scheme from the examples provided by Allergan on the basis that Allergan had provided no evidence that such composite schemes were in regular use by the pharmaceutical industry prior to 1 January 1993.

Further, the Panel assumed, from the market details provided that **many areas would have to increase their prescribing of Allergan's products in order to reach the first threshold and thus qualify for a rebate**. Four areas had signed up to the scheme of which two had unit shares above the first threshold one above the second threshold and the other just below the first threshold. The Panel considered that **insofar as the scheme encouraged the trust to persuade prescribers to increase their prescribing so that the trust could gain a cash rebate, or increase its cash rebate, it could be interpreted as an inducement'** (emphasis added).

Alcon alleged therefore that the scheme's structure (which was based on unit market share - meaning that it is necessary for the NHS organisation to displace competitors' products in order to benefit from the retrospective rebate) appeared to be another factor which the Panel took into account in deciding that the arrangement could not benefit from the Clause 1.2 exemption. Thus, Allergan's claim that its scheme achieved the same 'ultimate result' as a standard discount was incorrect. Whilst it was true that, as Allergan submitted that, a growth in demand for its products inevitably led to a decline in the demand for others, the way in which the scheme was structured meant that its psychological effect would be different to that of a standard discount scheme. As explained in Alcon's complaint, there would be particular areas with more than participating NHS organisation (London was one example); in such cases the risks associated with the scheme would be even more pronounced as organisations would compete with each other to meet the thresholds required to obtain the retrospective rebate for Allergan's glaucoma products. As one organisation would not know what threshold had been achieved by the other NHS organisation(s) in that area, it was likely to over-compensate by adopting strategies to significantly increase its own market share for Allergan products so that it was best placed to obtain the retrospective rebate itself. Alcon submitted that Allergan had likened the scheme to a patient access scheme but ignored cost comparisons and considerations of alternative therapies. The driver of the scheme would therefore be the rebate which could result in undue pressure being put onto prescribers who would have little understanding of the impact of their prescribing on achieving the overall threshold. In this respect it would be possible for them to 'over-prescribe' products within the scheme.

Alcon alleged that therefore, in spite of Allergan's insistence on the fact that the scheme was totally transparent, the need to attain a certain unit market share threshold created uncertainty (and would, in some circumstances, be dependant on the success of other NHS organisations within the same geographical area taking a share of the market for Allergan products). Indeed, as explained in Alcon's complaint, the risk associated with annual fund payments was that participating NHS organisations might be tempted to prescribe more Allergan products than was necessary to obtain the retrospective rebate because the long accounting period would give rise to uncertainty (notwithstanding the provision of quarterly reports showing unit market share).

Finally, Alcon noted that Allergan had commented

on the recent interest in patient access schemes and innovative flexible pricing schemes, none of which were identical to the schemes that were known in 1993. Allergan concluded that on the principles applied by the Panel in its ruling that Allergan's scheme breached the Code, all such schemes would also constitute such breaches. Allergan submitted that this could not be the right conclusion.

Alcon alleged that Allergan's comment was misleading. Indeed, Allergan misrepresented the implications of the Panel's ruling, jumping to the conclusion that all novel schemes (whether patient access schemes or innovative flexible pricing schemes) would breach the Code. Thus Allergan seemed to conclude that all schemes subject to the Code would also breach the Code; these were however two different issues which Allergan incorrectly conflated by concluding its discussion of the Clause 1.2 exemption with the above statement. In the present case, Alcon agreed with the Panel's ruling that Allergan's scheme was both subject to the Code and in breach of it (because it operated as an inducement to prescribe Allergan's glaucoma medicines). However, this was not to say that any novel scheme would be in breach of the Code; it would depend on the specific circumstances. For example, in the case of an outcome or risk sharing agreement, the PMCPA's guidance on 'Joint working and the ABPI Code of Practice for the Pharmaceutical Industry' provided that such arrangements are acceptable so long as certain conditions were met. In such cases, a refund or recompense paid to a health authority or trust would not constitute an inducement to prescribe because the company did not pay for prescriptions (rather, it provided a refund/recompense where the therapeutic effect did not meet expectations). Accordingly, the scheme did not benefit from the Clause 1.2 exemption and was subject to the Code.

The scope of the Clause 18.5 prohibition

Alcon noted that Allergan further submitted that even if the scheme was held to fall within the scope of the Code, it did not breach Clause 18.5 because the retrospective rebate did not constitute a donation or grant within the meaning of Clause 18.5 and, further, that clause prohibited only financial inducements to individual members of the health profession. Alcon's substantive comments on this point were set out below (Alcon strongly disagreed that Clause 18.5 was indeed limited in the ways Allergan argued). However, Alcon alleged that it first should be noted that the Clause 18.5 prohibition of inducements to institutions, organisations or relevant associations was not, as Allergan claimed 'expressly excluded' from the European legal framework (which had been transposed into English law). In this regard, Alcon's comments above applied concerning the relationship between the legal and self-regulatory regimes.

Breach of Clause 18.5

Alcon noted that Allergan's appeal on Clause 18.5 was focussed on the argument that the scheme did not fall within the scope of that clause. Allergan did not specifically address whether the scheme was an inducement in the event that the Appeal Board agreed with the Panel and with Alcon that Clause 18.5 was applicable to the arrangement.

Allergan disputed the Panel's characterisation of the retrospective rebate as a donation, grant or benefit in kind on the basis that it was a contractual payment which must be paid if certain target sales volumes were reached. Alcon alleged that firstly, and as explained below, the retrospective rebate was not given in isolation; as the Panel noted, Allergan provided a 'package of support' in addition to the retrospective rebate and, further, the scheme was composite in nature (retrospective cash rebate plus administration of subsequent trust fund). Therefore, Allergan oversimplified the Scheme by characterising it as a simple contractual payment; the scheme was in fact multi-faceted. Secondly, Allergan could not escape the scope of Clause 18.5 on the basis that the retrospective rebate - which itself triggered associated benefits - was given in exchange for the achievement of a certain unit market share for Allergan products. Indeed, the contractual promise of a retrospective rebate under the scheme was precisely one of the reasons why the scheme constituted an inducement to prescribe. NHS organisations were directly induced to prescribe/recommend/buy etc Allergan products - and to displace competing products - in order to obtain the retrospective rebate, the package of support and the means of developing ophthalmic services in the community.

Allergan also relied on the PMCPA's guidance which stated that: 'Clause 18.5 relates to donations and grants etc and not to activities involving the sale of medicines'. However, as noted above, that statement must be read in its proper context. The guidance in fact stated that Clause 18.5 would not impact upon joint working because it related to donations and grants and not to activities involving the sale of medicines; however, the guidance further stated that: 'If the company's medicines were not sold as part of the joint working, **Clause 18.5 might apply**' (emphasis added). As Allergan acknowledged, the present arrangements were clearly not part of joint working; therefore, in principle, Clause 18.5 was relevant (and, moreover, was applicable in the present case, as explained further below). The fact that activities involving the sale of medicines (ie under contractual arrangement) might fall within the scope of Clause 18.5 further supported the argument that Allergan could not escape liability on the basis that the retrospective cash rebate element of the scheme was given under a contractual obligation.

Allergan stated that the Panel's conclusion (that the scheme in effect could be seen as a donation, grant or benefit in kind) did not appear to be based on any preceding reasoning or evidence. However, Alcon alleged that the Panel's ruling in this respect was reasoned; the Panel noted that a package of

support was provided to the NHS organisation in addition to the cash rebate which was inextricably linked to the promotion of Allergan's glaucoma medicines. Further, the Panel's reasoning in respect of the Clause 1.2 exemption was also relevant in this regard. Indeed, and as discussed above, the Panel characterised the scheme as composite in nature because it consisted of a retrospective cash rebate and the administration of a trust fund. Thus it provided a collateral benefit ie the means '... to develop ophthalmic services in the community and or for the benefit of patients with ophthalmic conditions' as stated in the agreement (the fact that Allergan claimed to have no influence and, in most cases, no knowledge of the way in which the funds were used was not relevant to the Clause 18.5 assessment).

Allergan further submitted that Clause 18.5 (which was introduced in 2008) was not intended to create an entirely new obligation on ABPI member companies or others who had elected to be subject to the Code. According to Allergan, Clause 18.5 was a restatement and clarification of Clause 18.4 and – in order to be consistent with Clause 18.1 - should be interpreted as prohibiting only donations, grants and benefits in kind which constituted an inducement to individual members of the health profession. However, Allergan did not appear to have any basis for its assertion that Clause 18.5 was not intended to create an entirely new obligation; indeed, if it was not intended to create a new obligation, it would be redundant (the same applied for Clause 18.6). Further, the supplementary guidance to Clause 18.5 specifically stated that 'donations and grants to health professionals are not covered by this clause' (presumably because they were covered by Clause 18.1). Clause 18.5 clearly prohibited the provision of donations (etc) to institutions which constituted an inducement to that institution; it simply did not make sense to say that it prohibited donations which constituted an inducement to individual health professionals. Indeed, the concept of 'inducement' had no meaning within the context of Clause 18.5 unless the donee and the person induced were one and the same (namely, the institution).

For the sake of completeness, Alcon alleged that Allergan's specific comments on the inter-relation between Clauses 18.5, 18.4 and 18.1 were unfounded and did not support its argument that Clause 18.5 was limited to the inducement of individuals. Indeed, it appeared that Allergan had argued that because Clause 18.5 referred to Clause 18.4 (which in turn referred to Clause 18.1) that the Clause 18.5 prohibition on inducements was limited to the provision of inducements to individuals. However, Clause 18.4 was only relevant in defining the allowable purpose of medical and educational goods and services (MEGS). Accordingly, Clause 18.5 provided for the relevant part that the provision of MEGS in the form of donations, grants and benefits in kind were only allowed if 'they comply with Clause 18.4 or are made for the purpose of supporting research'. Accordingly, if such donations/grants/benefits in kind were not made for the purpose of supporting research, they must – under Clause 18.4 'enhance patient care, or benefit the NHS and maintain patient care'. Therefore, the reference to Clause 18.4 in Clause 18.5 was only of relevance in defining the allowable purpose of MEGS; it did not suggest that the prohibition on inducements was limited to its Clause 18.1 meaning (which the PMCPA had decided was not applicable in this case). Quite the contrary, Clause 18.5 specifically provided that MEGS in the form of donations, grants and benefits in kind were only allowed if 'they do not constitute an inducement to prescribe, supply, administer, recommend, buy or sell any medicine'. If as Allergan suggested Clause 18.5 should be interpreted as subsidiary to Clause 18.4/18.1, there would be no reason for the Code to specifically state that MEGS in the form of donations/grants/benefits in kind might not constitute an inducement to prescribe. Accordingly, by specifically stating that donations/grants/benefits in kind to institutions etc might not constitute an inducement to prescribe, the Code clearly prohibited inducements to such institutions.

Alcon alleged that offering an inducement to an NHS organisation, such as a PCT, might trigger that PCT to introduce financial inducement systems aimed at medical practices (which ultimately benefitted GPs who shared in the profits made by the practice). The ABPI had declared that the operation of such schemes by PCTs violated Article 94(1) of the Directive; the ABPI's case against the MHRA on this point was currently pending before the European Court of Justice.

Accordingly, Alcon alleged that as the Panel found, the scheme in effect operated as a kind of donation, grant or benefit in kind and should comply with Clause 18.5. However, the Scheme fell foul of Clause 18.5 because the retrospective rebate was inextricably linked to the promotion of Allergan's glaucoma medicines such that it amounted to an inducement to buy, recommend and prescribe those medicines.

Breach of Clauses 9.1 and 2

Alcon disagreed with Allergan's statement that if the Appeal Board ruled no breach of Clause 18.5 then the breaches of Clauses 9.1 and Clause 2 fell away. Nothing in the wording of either Clause 2 or Clause 9.1 suggested that they must be linked to other breaches of the Code. Clause 2 provided that 'Activities or materials associated with promotion must never be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry'. The clause was therefore very broadly worded and encompassed any activity/material 'associated with promotion'. Although Clause 2 was normally reserved for cases of particular censure and, for this reason, typically followed one or more other breaches of the Code, there was no reason why, in principle, Clause 2 could not be ruled in isolation or in conjunction with Clause 9.1. Even if the Appeal Board were to find that the scheme fell outside the

scope of the Code as a whole or outside the scope of Clause 18.5, it might nevertheless consider that the scheme constituted an unacceptable inducement to prescribe. Indeed, the scheme induced NHS organisations to displace competitors' products, by irrationally switching patients who were currently well controlled on a non-Allergan product to an Allergan-product, in order to obtain a retrospective rebate and associated package of support. As explained above, the scheme was structured to create uncertainty amongst NHS organisations and its psychological effect was very different from that of a standard discount/rebate. Thus, whether or not the Appeal Board considered that the scheme breached Clause 18.5, Allergan's activity should not be tolerated if it brought discredit upon, or reduced confidence in, the pharmaceutical industry. With regard to Clause 9.1, this was very broadly worded and not linked to any other provision in the Code ie 'High standards must be maintained at all times'.

Alcon noted that the Panel had previously found companies to be in breach of Clause 9.1, even where no other breach of the Code was ruled. By example in Case AUTH/2175/10/08 (Anonymous General Practitioner v ProStrakan) regarding an osteoporosis audit service; breaches of Clause 9.1 were ruled, but no other breach of the Code.

Alcon alleged that clearly, it was not compatible with high standards to operate a scheme which, as explained above, induced NHS organisations to displace competitors' products in order to obtain a retrospective rebate and associated package of support. Allergan's aggressive approach was evidenced by its briefing document for representatives. As explained above, this briefing document sets out 'Actions to get started'; step one stated that the formulary status of all three glaucoma products had to be determined and representatives were instructed that if one or more products was not on the formulary they must take 'immediate action to gain formulary listing'. Further, under 'Step two (primary care)', the representatives were instructed to assess the 'capability of commissioned organization to influence prescribing' (as explained above, this suggested that those organisations which could not influence prescribing should be excluded from the scheme). Alcon alleged that Allergan's assertion that the scheme did not require any of its products to be prescribed and that the decision rested with the individual clinician was disingenuous because, as explained above, an NHS organisation was required to attain a certain level of prescriptions, calculated as market share, in order to derive the real benefit from the scheme ie the retrospective rebate. Allergan effectively used the scheme to encourage NHS organisations to displace competing products, with the consequence that patients might not be prescribed the most appropriate medicine. Allergan referred to the DoH's document entitled 'Commercial sponsorship – ethical standards for the NHS' and cited the example of a situation where a manufacturer of a nicotine replacement therapy offered to provide its product at a reduced rate to a Health Action Zone or a health authority. In this context, Allergan quoted the DoH's statement that 'This arrangement is acceptable provided that there is a clear clinical view that that these products are appropriate to particular patients and there is no obligation to also prescribe these products to other patients for whom an alternative product would be equally beneficial'.

Alcon alleged, however, that the example concerned a standard discount where there was no inducement to prescribe; it was therefore not relevant to the present situation. The scheme, on the other hand, operated as an inducement with the consequence that the status quo (where clinicians had the discretion to prescribe the most appropriate product for the individual patient) was subverted. *De facto*, if an NHS organisation wanted to obtain the retrospective rebate (which was the only reason it would enter into the agreement with Allergan), it would be obliged to prescribe, or recommend for prescription, Allergan products to patients for whom an alternative product would be equally beneficial in order to meet the unit market share thresholds (or even to switch patients from another product that previously had been considered the appropriate treatment). Further, Allergan denied a breach of Clauses 9.1 and 2 on the arbitrary basis that interpretation of the Code was a difficult area and was not straightforward. Allergan submitted it would be unduly harsh to rule that if Allergan's interpretation was at odds with the Panel's this should constitute a failure to maintain high standards or actions likely to reduce confidence in the pharmaceutical industry. In Alcon's view application of Clauses 9.1 and 2 was not limited to straightforward breaches of the Code; the applicable standard was the severity of the conduct.

Alcon was concerned that Allergan's scheme would set a major precedent for the pharmaceutical industry and would imply to the medical community and the public that it was legitimate for pharmaceutical companies to pay for prescriptions. This would discredit the pharmaceutical industry and potentially cause a government backlash. Accordingly, in light of the above, Alcon maintained that Allergan's grounds of appeal were unfounded and should be rejected.

APPEAL BOARD RULING

The Appeal Board considered that although the scheme at issue contained elements of trade practices relating to prices, margins and discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993, and which were otherwise exempt from the Code, the way in which the scheme operated as a whole meant that it had gone beyond that exemption and was thus subject to the Code.

The Appeal Board noted that the scheme was based upon a volume based percentage market share ie the amount of rebate due depended upon the

number of bottles of Allergan products prescribed. This was confirmed by Allergan at the appeal. The Appeal Board further noted that the representatives' briefing material stated that the territory managers would support participating units with appropriate educational events and meetings. Alcon however, confirmed at the appeal that it had no evidence to show that the provision of educational events and meetings was exclusively linked to the retrospective rebate scheme.

The Appeal Board considered the applicability of Clause 18.5 and noted that in its view the rebates paid were a contractual financial arrangement. The amount paid was conditional on obtaining certain thresholds of market share. In that regard the Appeal Board did not consider that the rebate was a medical and educational good or service in the form of a donation, grant or benefit in kind. The Appeal Board thus ruled no breach of Clause 18.5.

The Appeal Board was concerned that the scheme could be perceived as an inducement to prescribe Allergan's products. The Appeal Board noted that generally such schemes might result in more prescriptions of a company's product. That was not necessarily unacceptable as long as the arrangements complied with the Code. The question to be established was whether the scheme amounted to an inappropriate inducement. A primary care organisation would potentially qualify for a larger cash rebate if its prescribers increased the number of packs of Allergan products they prescribed. Whilst it was true that one way to do this would be to switch from another company's medicines, nonetheless, the Appeal Board noted that there was no evidence of undue pressure on individual prescribers to do this. On the merits of this particular case the Appeal Board decided that Allergan had not failed to maintain high standards. No breach of Clause 9.1 was ruled. The Appeal Board subsequently ruled no breach of Clause 2. The appeal was successful on all points.

Complaint received **7 October 2009**

Case completed **24 February 2010**

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During its consideration of this case the Panel sought advice from Mr Alan Sheppard, BTech (Hons), Managing Director, Ascher Resources Ltd, who provided an opinion in a personal capacity.

CASE AUTH/2273/10/09

LILLY v NOVO NORDISK

Victoza launch

Lilly complained about promotional and press materials issued to mark the launch of Victoza (liraglutide) by Novo Nordisk. Allegations were also made about patient support materials. Lilly made many repetitive allegations and they are not all repeated in this summary. The detailed complaint from Lilly is given below.

Victoza was a once daily, human glucagon-like peptide (GLP)-1 analogue. It was indicated for the treatment of type 2 diabetes to achieve glycaemic control firstly in combination with metformin or a sulphonylurea in patients with insufficient glycaemic control despite maximally tolerated dose of monotherapy with metformin or a sulphonylurea. Secondly in combination with metformin and a sulphonylurea or a thiazoldinedione in patients with insufficient glycaemic control despite dual therapy. Byetta (exenatide), was a twice daily GLP-1 analogue, marketed by Lilly, licensed for second-line use with sulphonylureas or metformin.

With regard to public relations materials Lilly referred to seven articles (including one television and one radio interview) in the lay and health professional media. Lilly was concerned that the articles implied that Victoza was to be used for weight loss or reductions in blood pressure (BP) rather than its licensed indication. Lilly alleged that the overwhelming emphasis on weight reduction was likely to raise unfounded hopes of successful treatment. The same could be said of the implied claim of protection against heart disease by virtue of Victoza's effect on BP. Lilly alleged breaches of many clauses of the Code including a failure to provide details of precautions and side effects.

The detailed response from Novo Nordisk is given below.

In considering the allegations about articles/interviews in the media the Panel examined the press materials provided by Novo Nordisk, not the articles/interviews per se. The media backgrounder package comprised seven documents including one on 'Incretins' and another on 'Victoza (liraglutide)'. There was also a lay press release and a medical press release. The Panel considered that as the press pack did not include details of precautions or side effects it was likely to mislead as to the overall benefits of Victoza. Breaches of the Code were ruled.

The Panel was concerned that the overall impression of the press pack was that Victoza was to be prescribed to control blood glucose, reduce weight, reduce BP and improve β-cell function. The materials were not clear regarding the licensed indication as set out in the summary of product characteristics (SPC). The press pack placed equal emphasis on the pharmacodynamic information set out in the SPC with regard to reductions in weight and BP and improved β-cell function. Readers might be confused as to the precise indication for Victoza. Little mention was made that Victoza was only to be prescribed as combination therapy when first and/or second line oral treatment failed to produce adequate glycaemic control.

The Panel ruled that the backgrounders 'Incretins' and 'Victoza (liraglutide)' were misleading with regard to the licensed indication and inconsistent with the SPC. On appeal by Novo Nordisk the Appeal Board ruled no breach of the Code.

The Panel ruled that the 'Incretins' backgrounder was misleading, exaggerated and not capable of substantiation with regard to its emphasis on weight reduction which had not been quantified. The SPC stated that weight reduction was between 1kg and 2.8kg and the data was less positive for 1.2mg Victoza in that mean body weight increased by 0.23kg in the 1.2mg Victoza and glimepiride group. On appeal by Novo Nordisk the Appeal Board upheld the Panel's ruling that the 'Incretins' backgrounder was not capable of substantiation.

The 'Victoza (liraglutide)' backgrounder quantified the weight loss data but did not include the weight gain data from the SPC. The Panel ruled that the backgrounder was misleading, not capable of substantiation and exaggerated as it did not reflect the totality or limitations of the data. On appeal by Novo Nordisk, the Appeal Board ruled no breach.

The Panel ruled breaches as the 'Incretins' and 'Victoza (liraglutide)' backgrounders were not presented in a balanced way and would raise unfounded hopes of successful treatment. The Panel ruled no breach in that these backgrounders were not promotional material as such and were not disguised promotion.

With regard to statements about BP the Panel noted that the backgrounders referred to reductions in systolic blood pressure (SBP). Section 5.1 of the SPC stated that Victoza decreased SBP by an average of 2.3 to 6.7mmHg from baseline and compared to active comparator the decrease was 1.9 to 4.5mmHg. The available data was for no longer than 26 weeks and related

only to certain combinations of liraglutide and oral antidiabetic (OAD) agents.

The 'Incretins' backgrounder stated that liraglutide's impact on, *inter alia*, reduction in SBP had been consistently demonstrated throughout the phase 3a LEAD (Liraglutide Effect and Action in Diabetes) trials. The reduction was not quantified and nor was any benefit claimed for the reduction. There was no claim implied or otherwise regarding protection against heart disease as alleged and thus no breach was ruled. A similar ruling was made regarding the 'Victoza (liraglutide)' backgrounder. The Panel ruled no breach of the Code in relation to allegations that the media articles claimed Victoza helped patients stay off insulin treatment and disparaged insulin treatment. These rulings applied to the backgrounders 'Incretins', 'Victoza (liraglutide)', 'Diabetes treatment' and 'Facts about type 2 Diabetes Treatment' and the press releases.

The Panel considered that the data regarding weight loss in both the lay and medical press releases were misleading, constituted a misleading comparison and were not capable of substantiation. Breaches were ruled. Upon appeal by Novo Nordisk of these two rulings the Appeal Board did not consider that the weight loss data in the press releases was incapable of substantiation or constituted a misleading comparison and ruled no breach in these regards. The press releases exaggerated the position and a breach was ruled. The Panel considered that a quotation in the press release that '… patients with type 2 diabetes can be confident they are controlling their blood sugar, and may benefit from weight loss. This is an important advance for patients with type 2 diabetes, many of whom are already overweight' implied that if patients on liraglutide lost weight the amount lost meant that they would no longer be overweight. This was not so. Breaches were ruled. One of these rulings was appealed by Novo Nordisk. The Appeal Board considered that the claim was capable of substantiation and no breach in that regard was ruled. The Panel considered that the quotation was misleading in referring to Victoza being an important advance with regard to the potential weight loss benefit and ruled a breach. The Panel, however, did not consider that the claim disparaged Byetta and thus ruled no breach in that regard.

The Panel did not consider that the references to the benefit of a reduction of SBP in either press release were unacceptable; no benefit for the reduction was claimed or implied. No breach was ruled.

The Panel ruled that the press releases were inconsistent with the SPC and were misleading with regard to the licensed indication. Upon appeal by Novo Nordisk, the Appeal Board ruled no breach.

The Panel considered that the inclusion of the very positive claims in the lay press release and the lack of information about side effects etc in effect turned the lay press release into an advertisement for a prescription only medicine and a breach was ruled. Upon appeal by Novo Nordisk, the Appeal Board ruled no breach.

The Panel considered that the press releases were not factual or balanced and would raise unfounded hopes of successful treatment particularly with regard to weight loss. Statements had been made in the lay press release to encourage the public to ask their health professional for Victoza. Each was ruled in breach.

Neither one of the opinion leaders quoted in one of the articles at issue nor a pharmacist quoted in another was a Novo Nordisk spokesperson. The Panel did not know if the pharmacist had been provided with a press pack. The Panel decided that on the information before it Novo Nordisk was not responsible under the Code for the comments attributed to either person and no breach was ruled.

In an interview, a health professional briefed by Novo Nordisk to give interviews in relation to the Victoza launch, stated that Victoza had undergone 'one of the most extensive programmes of development that we've seen in diabetes, probably well over ten years …'. In the Panel's view this implied that Victoza had undergone a more extensive development programme than other antidiabetic medicines. There was no information before the Panel to substantiate this implied comparison which was ruled in breach as it was misleading, not capable of substantiation and disparaged other medicines.

The Panel considered that other statements, that the risk of developing hypoglycaemia was extremely low, were misleading with respect to the safety of Victoza and breaches were ruled. The Panel further noted that in response to the question 'And how long has it been trialled for? There's a lot of concern sometimes about side-effects' the health professional did not refer to the side effect profile of Victoza, in particular he did not discuss the common or very common gastrointestinal effects of the medicine. The Panel ruled a breach as the answer to the question was misleading by omission.

The health professional stated that Victoza might stop type 2 diabetes progressing and stop the likelihood of patients needing to go onto insulin. There was no data before the Panel to show that this was so. Although β-cell function improved with Victoza it had not been demonstrated that patients would not need to progress onto insulin therapy. The Panel ruled breaches as the statement was misleading and exaggerated.

The Panel did not consider that it was inconsistent with the Authority's Constitution and

Procedure for Novo Nordisk to provide the health professionals used at the launch with details of Lilly's complaint which Lilly alleged was an attempt by Novo Nordisk to tarnish Lilly's reputation. The Panel had not been given details of what Novo Nordisk had provided to these health professionals. As a principle it was not necessarily unacceptable under the Code. The Panel considered that Lilly had not proven its allegation on the balance of probabilities. No breach was ruled including Clause 2.

Lilly had referred to the media activity in total and alleged breaches including Clause 2.

With regard to these general allegations and the press materials referred to above, the Panel considered that high standards had not been maintained and a breach was ruled. With regard to Clause 2, which was used as a sign of particular censure, the Panel considered that issuing misleading material to the press was a serious matter as was issuing a press release that advertised a prescription only medicine to the public. The Panel thus ruled a breach of Clause 2. Upon appeal by Novo Nordisk the Appeal Board, although concerned about the material, overturned this ruling.

With regard to the journal advertisements and other promotional material Lilly was concerned, *inter alia*, that the material was inconsistent with the Victoza SPC and implied that it could be used as a treatment for obesity and hypertension. Claims for weight loss, reductions in BP and changes in β-cell function could not be substantiated. The promotional material implied that Victoza delayed the progression of type 2 diabetes. The material was alleged to be misleading about side effects and the dosing of Victoza. Breaches of many clauses, including Clause 2, were alleged.

The Panel considered that the heading to a journal advertisement 'Do more than lower blood glucose' encouraged Victoza to be prescribed because of its effects beyond that of glycaemic control. In that regard the benefits of therapy had not been separated from or placed subsidiary to the main indication. A wider indication was implied. The reason to use Victoza, ie to reduce HbA1c, was the third piece of information on the page after the heading and the subheading which stated that 'Once-daily Victoza … impacts on multiple factors associated with type 2 diabetes …'. In boxed text equal emphasis was given to 'Reductions in HbA1c' as to reductions in weight, SBP and improvements in β-cell function.

The Panel considered that the secondary effects on weight, SBP and β-cell function had not been placed sufficiently within the context of the primary reason for prescribing Victoza (glycaemic control) or within the limit of the data. This was inconsistent with the SPC and a breach was ruled. Upon appeal by Novo Nordisk the Appeal Board overturned the ruling as it considered the advertisement was not inconsistent with the Victoza SPC.

The Panel did not consider that the advertisement invited a comparison with other antidiabetic medicines. It suggested that Victoza offered more than lowering of blood glucose but this was not necessarily unacceptable or disparaging. No breach was ruled.

The Panel considered the claim, 'Reductions in weight', too simplistic given the data. Although weight loss would benefit type 2 diabetics, the amount lost was small. Nonetheless some weight loss, however modest, was preferable compared with the weight gain associated with some other antidiabetic treatments. The SPC recorded weight gain data for Victoza 1.2mg plus glimepiride. It was important for health professionals to fully understand the magnitude of weight loss with Victoza and that not every patient would lose weight. This was not possible from the claim at issue. The Panel considered that the claim was misleading, ambiguous and exaggerated; it could not be substantiated for each Victoza dose (1.2mg or 1.8mg) or licensed combination. Breaches were ruled. Upon appeal by Novo Nordisk the Appeal Board overturned the Panel's rulings as it did not consider the claim was misleading or incapable of substantiation or exaggerated.

The BP changes had not been quantified in the advertisement. The claim 'Reductions in systolic blood pressure' implied that this applied to every licensed combination and was clinically and statistically significant. The SPC only referred to reductions in SBP vs active comparator and some of the results had not been statistically significantly different to placebo. It was important that health professionals fully understood the effects on BP. This was not possible from the claim at issue. The Panel ruled that the unqualified and unquantified claim was misleading, ambiguous and exaggerated and could not be substantiated. Breaches were ruled. Upon appeal by Novo Nordisk the Appeal Board overturned the Panel's rulings as it did not consider that the claim was misleading, ambiguous and exaggerated and it could be substantiated.

The Panel did not consider that the lollipop tree visual implied that Victoza could uproot type 2 diabetes and eliminate the illness. In the Panel's view it illustrated that there were a number of factors linked to type 2 diabetes. The Panel did not consider the visual was, in itself, inconsistent with the SPC as alleged and no breach was ruled.

The Panel considered that high standards had not been maintained; a breach was ruled which was overturned on appeal. The Panel did not consider the circumstances warranted a ruling of a breach of Clause 2.

The Panel considered that the claim 'SMC Pending' (Scottish Medicines Consortium) used on a reprint folder strongly implied that SMC approval was a formality or a matter of time rather than reflecting that Victoza at the time was going through the SMC process. The Panel ruled that the claim was ambiguous and thus misleading. The Panel considered that the SMC's active consideration of the product was sufficient with regard to the requirement to provide substantiation. The claim did not exaggerate the position nor was it a claim for a special merit. No breach was ruled. The Panel ruled no breach with regard to the allegation that Novo Nordisk had reproduced an official document without permission. The Panel did not consider that the use of the phrase 'SMC Pending' warranted a ruling of Clause 2.

The Panel did not consider that a claim in two leavepieces 'Victoza + metformin provide significant reductions in HbA1c compared with metformin alone …' was misleading given the published data. However, an explanation of statistical significance vs metformin in the leavepieces was ruled to be misleading in that every combination included metformin.

The Panel ruled breaches as it considered a chart in the leavepieces was misleading in that only the results for patients pretreated with OAD monotherapy were shown. The Panel considered that the data had been cherry-picked to show the results which demonstrated the largest positive difference for Victoza. Further breaches were ruled. The Panel considered that the positioning and presentation of a claim 'p<0.0001 versus metformin' reinforced the misleading impression of a statistically significant difference between the Victoza + metformin and the glimepiride + metformin data which was ruled to be misleading. The presentation of the data was inconsistent with the SPC and a breach was ruled. Upon appeal by Novo Nordisk, the Appeal Board overturned this ruling.

The Panel noted that a claim 'Statistically, fewer minor hypoglycaemic events were observed with Victoza in combination with metformin compared to metformin in combination with glimepiride (p<0.001)', reflected data from the LEAD 2 study and the SPC. In that regard the Panel did not consider that the claim was misleading. However, in the Panel's view, a claim 'In a separate study, no major hypoglycaemic events were observed with Victoza in combination with metformin and a thiazolidinedione' sought to minimize a clinician's concerns regarding the occurrence of hypoglycaemia in this treatment group. The SPC listed hypoglycaemia as common in patients being so treated. Omission of this data, given the inclusion of data about major hypoglycaemia, was ruled to be misleading.

Page 3 of the leavepieces presented the weight loss data for Victoza 1.2mg in combination with metformin although, as before, the heading and subheading did not make it clear that the results were for one dose of Victoza only. The Panel noted that the weight loss shown for Victoza plus metformin was within the range stated in the general comment in the SPC that sustained weight reduction over the duration of studies ranged between 1kg to 2.8kg (both 1.2mg and 1.8mg Victoza doses) and no breach was ruled. The Panel did not consider that the reference to early weight loss and the absence of p values in this regard implied a statistically significant difference as alleged and ruled no breach. The Panel ruled no breach with regard to absence of data for baseline body weight and the incidence of nausea, diarrhoea, vomiting, dyspepsia or visceral fat. The Panel did not consider the leavepiece was disparaging with regard to visceral fat data. Lilly had not made a detailed allegation in this regard. No breach was ruled.

The Panel considered that overall the leavepieces failed to maintain high standards and a breach was ruled. The Panel did not consider that the leavepieces warranted a ruling of a breach of Clause 2.

Pages 2 and 3 of two other leavepieces did not distinguish between the licensed indication and the benefits set out in the pharmacodynamics section of the Victoza SPC. On balance the Panel ruled that the data were presented in a misleading manner in that it appeared all the data was covered by the indication for Victoza and this was not so. A breach of the Code was ruled. The Panel did not consider that the data, in effect, promoted Victoza for unlicensed indications and thus no breach was ruled in that regard. The Panel did not consider that the leavepieces accurately reflected the balance of evidence as stated in the SPC with regard to major hypoglycaemic events and breaches were ruled. The Panel considered that although a complex table of data in the leavepieces would need to be read carefully to be understood, it was not misleading per se to omit the baseline data as alleged by Lilly. No breach was ruled. The Panel did not consider that the leavepieces were disparaging as alleged and no breach was ruled.

With regard to the claim in a leavepiece 'Dosing: use one device, once a day' the Panel considered that the front page of the leavepiece was not sufficiently clear that Victoza was to be used in combination with OADs rather than as monotherapy. The claim was misleading and the Panel's ruling of a breach of the Code was upheld on appeal by Novo Nordisk.

The Panel considered the claim 'Victoza allows convenient once-daily dosing at any time independent of meals' was ambiguous and misleading given the specific mention in the SPC that '… it is preferable that Victoza is injected around the same time of day, when the most convenient time of day has been chosen'. Upon

appeal by Novo Nordisk the Appeal Board overturned the Panel's ruling.

With regard to page 2, the Panel noted that it was stated that when Victoza was administered with metformin or with metformin plus a thiazolidinedione, no dose adjustments were needed. This was in line with the SPC and no breach was ruled.

The Panel ruled that high standards had not been maintained. The Panel was concerned that the leavepiece was not clear about the indications for a new product and implied that it could be used as monotherapy. The Panel decided on balance that the leavepiece brought discredit upon the industry and a breach of Clause 2 was ruled. Upon appeal by Novo Nordisk the Appeal Board overturned both of the Panel's rulings.

Lilly alleged that a patient booklet promoted Victoza to the public. It included the brand name no less than eighty-nine times and included promotional messages and minimised the risk of hypoglycaemia. Similar allegations were made about a patient website.

The Panel was concerned that the front page of the patient booklet included the product logo plus the claim 'New' which implied that the content was promotional. This impression was compounded by the positive statement 'Making a fresh start with Victoza'. Such promotional branding combined with a claim should not be used in patient materials. In the Panel's view the front page was, in effect, an advertisement for a prescription only medicine to the public and a breach was ruled. This ruling was upheld on appeal by Novo Nordisk.

The Panel did not consider that it was unacceptable to refer to NovoFine and NovoTwist needles in relation to the section 'Prepare your pen' and no breach was ruled.

The Panel considered that to state in the patient booklet that the risk of hypoglycaemia was minimised with Victoza was not fair or balanced; it misled with regard to the safety of the product and a breach was ruled.

Page 8 stated 'You should inject Victoza only once a day, at any time of day, with or without eating food first. But it's best if you use Victoza at the same time every day – so pick a time you won't forget'. The Panel did not consider that this page of the booklet promoted Victoza to the public as alleged. The information was in line with the SPC and no breach was ruled.

The Panel did not consider that the statement on page 18 'Here are a few tips to help you fit Victoza into your life better' was a promotional claim. This section referred to the need to take medicine regularly in order to get the full benefits and referred readers to sources of help. The Panel did not consider that the page advertised Victoza to the public. Readers would have been prescribed the product. The information was not unreasonable. The Panel ruled no breach.

The Panel noted its ruling of a breach in relation to the front page. However, the Panel did not consider that overall the booklet was promotional material that had been disguised as information to patients and ruled no breach.
The Panel ruled that the use of the Victoza logo and the claim 'new' meant that high standards had not been maintained. The Panel did not consider that on balance the circumstances warranted a ruling of a breach of Clause 2.

With regard to the patient website the Panel noted the comments it had made about the patient booklet at issue above. The Panel noted that many of the webpages now at issue included the brand logo. The Panel considered that this was unacceptable and constituted the promotion of a prescription only medicine to the public. A breach was ruled. The Panel considered that in this regard high standards had not been maintained and a breach was ruled. Upon appeal by Novo Nordisk the Appeal Board overturned the Panel's rulings as it did not consider the webpages constituted the promotion of a prescription only medicine to the public and that high standards had not been maintained. The Panel did not consider that overall the webpages were promotional material that had been disguised as information to patients. No breach was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.

With regard to a formulary pack, Lilly made similar allegations to some of the allegations made about other promotional materials to health professionals.

The Panel considered that the purpose of Section 1 of the formulary pack overall was, *inter alia*, to establish a need for the additional benefits which might be provided by Victoza and to state where current therapies failed. The challenge of body mass index (BMI) and weight was given equal emphasis to glycaemic control. The Panel considered that the section implied that Victoza would positively address all of the unmet challenges. The Panel noted its comments and rulings above on Victoza's effect on secondary benefits. Breaches were ruled.

The Panel considered that the description of the unmet challenges in type 2 diabetes treatment in Section 1.6 'Unmet challenges' and Section 1.8 'Conclusion' could imply that no product currently available met any one of these challenges. The Panel considered that this was misleading as the challenges and the differences between current treatments were not defined in detail. The section disparaged current treatments and the impression given was not capable of substantiation. Breaches were ruled.

The Panel noted that Victoza was described as 'the first once-daily human glucagon-like peptide-1 (GLP-1) analogue developed for the treatment of T2D' in Section 1.7. The Panel noted, however, that although Victoza was the first once daily human GLP-1 analogue it was in fact the second GLP-1 analogue to be marketed. In that regard the Panel considered that the statement was ambiguous and thus misleading. It was unclear as to which part of the statement 'first' applied to. A breach was ruled which, on appeal by Novo Nordisk, was overturned by the Appeal Board.

The Panel ruled that high standards had not been maintained. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.

The Panel considered that in Section 2.1 the bullet point 'Liraglutide is administered once daily, and can be given at any time of day, independently of meals …' was similar to a claim at issue above in that the detailed advice in the SPC that '… it is preferable that Victoza is injected around the same time of day, when the most convenient time of day has been chosen' was not included. The Panel therefore ruled a breach which, on appeal by Novo Nordisk, was overturned by the Appeal Board.

The Panel noted that in Section 2.1 the second bullet point referred to Victoza's indication and the sixth bullet point referred to improvements in glycaemic control; this was immediately followed by another bullet point 'Significant weight loss in comparison with comparator drugs when liraglutide was used in combination treatment'. Section 2.4 'Indication and dosing' clearly set out the approved indication. The Panel noted that Section 2.5 'The LEAD Programme' ended with the sentence 'The clinical benefits of treatment with liraglutide observed with LEAD trials are reported here'. A section 2.5.1 'Liraglutide and glycaemic control' was immediately followed by Section 2.5.2 'Liraglutide and body weight'. Section 2.5.3 'Liraglutide and SBP' referred to reductions in BP. The Panel considered that although the approved indication was given almost at the outset of Section 2 ie glycaemic control, additional benefits of therapy (effect on body weight and BP) were given equal emphasis. They were not unequivocally distinguished from the main goal of therapy. In that regard the Panel did not consider that the secondary benefits were adequately placed within the context of Victoza licensed indication. A breach was ruled. Upon appeal by Novo Nordisk the Appeal Board overturned this ruling.

The Panel did not consider that Section 2.3 implied that only Victoza improved β-cell function as alleged and no breach was ruled. The Panel was concerned, however, that the discussion about β-cell function did not explain the clinical significance of the findings. Although Victoza had been shown to improve β-cell function there was no data to show that this altered the clinical course of type 2 diabetes; some readers might assume that the data meant that Victoza delayed or halted its progression. In this regard the Panel considered that the information given was misleading and that its clinical importance had been exaggerated and breaches were ruled. The Panel did not consider that failure to specifically mention Byetta's effect on β-cell function in Section 2.3 of the formulary pack was in itself misleading and no breach was ruled.
Section 2.5, 'The LEAD Programme', stated that Buse *et al* (LEAD 6) was the first study to directly compare the two GLP-1 receptor agonists and that the study compared 1.8mg liraglutide added to metformin and/or glimepiride vs 10mcg exenatide. The Panel did not consider that Section 2.5 was misleading as alleged. The limited information about Buse *et al* (LEAD 6) did not claim differences between the products, it merely listed this study as contributing to the clinical data. No breach was ruled.

The Panel noted that Section 2.5.5.1' 'Hypoglycaemia', went into more detail than Section 2.5 in relation to outcomes from Buse *et al* (LEAD 6). The Panel considered that more information should have been included – particularly with regard to the doses of Victoza and Byetta used and the fact that the study was open label. Insufficient detail had been provided and thus the claim regarding differences in hypoglycaemia was misleading. Breaches were ruled. Upon appeal by Novo Nordisk the Appeal Board overturned these rulings.

Section 2.5.5.2 'Adverse events' included details of the data for nausea from the LEAD studies. The Panel did not consider the claim that nausea persisted longer with exenatide than liraglutide implied that no patient experienced nausea at 26 weeks. A preceding sentence described it as one of the most frequently reported adverse events. No breach was ruled.

The Panel did not consider that Section 2.6 would mislead readers to consider liraglutide as a licensed treatment for hypertension and obesity as alleged. No breach was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach was ruled. Upon appeal by Novo Nordisk the Appeal Board overturned this ruling. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.

The Panel noted that Section 3.1 included the claims that liraglutide was 'cost-effective compared with glimepiride when added to metformin monotherapy and with rosiglitazone when added to glimepiride monotherapy. The basis for these calculations was given in Tables 3.2 and 3.3. The clinical inputs 'Change in HbA1c', 'Change in SBP' and 'Change in BMI' were listed

in each table. Table 3.2 was based on a sub group of patients from Nauck *et al* (LEAD 2). The BMI data was not given in Nauck *et al* (LEAD 2). The Panel noted the comments it had made about Nauck *et al* (LEAD 2) when considering the journal advertisement.

The Panel considered that Tables 3.2 and 3.3 implied that the indications for Victoza included decreasing weight and SBP. This was not so. Section 3.1 of the formulary pack did not make the licensed indication clear nor the magnitude of the weight reduction and BP data. The material was incomplete thus misleading as alleged and breaches were ruled. Upon appeal by Novo Nordisk the Appeal Board overturned these rulings.

The Panel considered that, in the context of a health economic evaluation, Section 3.6 was not misleading with regard to the timing of administration of Victoza. The important consideration for an economic evaluation was the once-daily administration of Victoza and not that it had to be administered at about the same time each day. No breach was ruled.

Section 3.6 stated that the cost of self monitoring of blood glucose (SMBG) was added where necessary. It also stated that 'SMBG is not needed in order to adjust the dose of liraglutide. Therefore initiating liraglutide before a treatment that does require SMBG will have a favourable cost implication'. The Panel noted Lilly's view that the statement appeared to ignore the fact that when Victoza was started the majority of patients would already be on treatments that required SMBG. The section implied that liraglutide would be used prior to a sulphonylurea. The Panel considered that there might be a theoretical cost benefit but this was not made clear. A breach was ruled.

Section 3.8 'Number needed to treat one patient successfully to target' included results from a meta-analysis comparing patients treated to <7.0% HbA1c, <130mmHg SBP with no weight gain. The Panel noted that the composite endpoint had been made clear and was relevant to diabetic patients. The SPC included data for changes in weight and BP. The Panel considered that this section was not misleading with regard to the licensed indication as alleged. No breach was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach was ruled. Upon appeal by Novo Nordisk the Appeal Board overturned this ruling. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.

At the completion of its consideration of this case, the Appeal Board was concerned about the presentation of the complaint. The Appeal Board deplored the way the complaint had been constructed with so many repetitive allegations. The response to the complaint could also have been better constructed; however some of the problems were as a direct result of the nature of the complaint. The time taken by the Panel and the Appeal Board to consider this case could have been substantially reduced if the complaint had been better presented.

Eli Lilly & Company Limited complained about Novo Nordisk Limited's launch activities for Victoza (liraglutide).

Victoza was licensed to treat type 2 diabetes mellitus to achieve glycaemic control firstly in combination with metformin or a sulphonylurea in patients with insufficient glycaemic control, despite maximal tolerated dose of monotherapy with metformin or sulphonylurea. Secondly, in combination with metformin and a sulphonylurea or a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.

Lilly's product Byetta (exenatide) was licensed for the treatment of type 2 diabetes mellitus in combination with metformin and/or sulphonylureas in patients who had not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

Both products were glucagon-like peptide-1 (GLP) analogues. Victoza was administered once daily whereas Byetta was administered twice daily.

To improve gastrointestinal tolerability the starting dose of Victoza was 0.6mg daily to be increased to 1.2mg after at least one week. Some patients were expected to benefit from an increase in dose from 1.2mg to 1.8mg to further improve glycaemic control. Victoza could be administered once daily at any time however it was preferable to inject around the same time of the day.

Section 5.1 of the Victoza summary of product characteristics (SPC), pharmacodynamic properties, stated that Victoza stimulated insulin secretion in a glucose-dependent manner. Simultaneously, it lowered inappropriately high glucagon secretion, also in a glucose-dependent manner. Thus, when blood glucose was high, insulin secretion was stimulated and glucagon secretion was inhibited. Conversely, during hypoglycaemia liraglutide diminished insulin secretion and did not impair glucagon secretion. The mechanism of blood glucose lowering also involved a minor delay in gastric emptying. Liraglutide reduced body weight and body fat mass through mechanisms which involved reduced hunger and lowered energy intake.

Section 5.1 of the SPC also included additional information about the product in relation to, *inter alia*, glycaemic control, beta-cell function, body weight and blood pressure. With regard to body weight the SPC stated that Victoza in combination with metformin, metformin and glimepiride or metformin and rosiglitazone was associated with

sustained weight reduction over the duration of studies in a range from 1kg to 2.8kg. Larger weight reduction was observed with increasing body mass index (BMI) at baseline. The results from studies lasting 26 weeks were included in the SPC. The weight reduction data included in the SPC was as follows:

Metformin add-on therapy	1.8 mg liraglutide + metformin	1.2 mg liraglutide + metformin	placebo + metformin	Glimepirde + metformin
N	242	242	240	121
Mean body weight (kg)				
Baseline	88.0	88.5	91.0	89.0
Change from baseline	-2.79	-2.58	-1.51	0.95

Glimepiride add-on therapy	1.8 mg liraglutide + glimepiride	1.2 mg liraglutide + glimepiride	Placebo + glimepiride	rosiglitazone + glimepiride
N	231	234	228	114
Mean body weight (kg)				
Baseline	83.0	80.0	81.9	80.6
Change from baseline	-0.23	0.32	-0.10	2.11

Metformin + rosiglitazone add-on therapy	1.8 mg liraglutide + metformin + rosiglitazone	1.2 mg liraglutide + metformin + rosiglitazone	Placebo + metformin + rosiglitazone	N/A
N	178	177	175	
Mean body weight (kg)				
Baseline	94.9	95.3	98.5	
Change from baseline	-2.02	-1.02	0.60	

Metformin + glimepiride add-on therapy	1.8 mg liraglutide + metformin + glimepiride	N/A	Placebo + metformin + glimepiride	insulin glargine + metformin + glimepiride
N	230		114	232
Mean body weight (kg)				
Baseline	85.8		85.4	85.2
Change from baseline	-1.81		-0.42	1.62

The SPC stated that over the duration of the studies Victoza decreased the systolic blood pressure on average by 2.3 to 6.7mmHg from baseline and compared to active comparator the decrease was 1.9 to 4.5mmHg.

The items at issue were considered as follows:

A Public Relations Activity

Lilly alleged that Novo Nordisk, through its agents and spokespersons, distributed inaccurate and misleading information about liraglutide to the UK consumer and medical press as evidenced by the articles and interviews which appeared in the Mail Online, Telegraph.co.uk, BBC Radio Ulster, ITV, the Pharmaceutical Journal, Clinical Pharmacist and the British Journal of Cardiology. Lilly believed that this coverage of liraglutide and its role in the management of type 2 diabetes was the result of inaccurate and misleading media and speaker briefing materials provided by Novo Nordisk. This assertion was based upon the consistency of the messaging supporting liraglutide as reported by the media and those that appeared in promotional materials. In inter-company dialogue Novo Nordisk acknowledged that before the launch of Victoza it had approached three of the health professionals referred to by Lilly to determine their willingness to provide their professional views and opinion on the product. Thus, contrary to Novo Nordisk's suggestion, the involvement of these health professionals was clearly not entirely independent. The company would have known their opinions about liraglutide; this was material to the fact that all of the health professionals mentioned by Novo Nordisk were then involved in public relations activities, supporting the launch of Victoza. Lilly asserted that the co-ordination and briefing was undertaken either by Novo Nordisk and/or its third party agent. Indeed, if Novo Nordisk and/or its agent(s) did not brief its spokespersons, as was suggested in inter-company dialogue, then this was clearly inconsistent with the Code.

From the coverage of liraglutide in the consumer and medical press Lilly believed it was likely that the media and speaker briefings had been held to advertise and promote the availability of liraglutide, a prescription only medicine, to the general public and to health professionals. Based on the articles, Lilly alleged that the information provided by Novo Nordisk was not entirely factual, misleading, employed sensationalist and promotional language and was not balanced or appropriately measured. Lilly was particularly concerned that the coverage in the consumer press was misleading regarding the precise licensed indication of liraglutide and its safety. The coverage raised unfounded hopes of successful treatment with respect to the unbalanced and often unqualified discussion of weight loss and blood pressure reductions associated with liraglutide which encouraged members of the public to ask doctors to prescribe liraglutide. Further, audiences were misled about the product's licensed indication and in this regard the activities and materials which supported the launch of liraglutide did not encourage its rational use.

Novo Nordisk stated that in inter-company correspondence Lilly named six independent health professionals and alleged that through these agents Novo Nordisk provided misleading and inaccurate information to the press. As Novo Nordisk highlighted to Lilly, only three of the named health professionals were contacted by Novo Nordisk before the launch of liraglutide in order to determine their willingness to provide their own

independent professional views on the compound to potentially interested lay and medical press journalists. As seen from the briefing materials, together with the practical information provided in advance of the interviews a script was not included as to what should be included in the interviews. The information communicated by these journalists was their own professional independent opinion based on their extensive clinical and practical experience with diabetes and the product gained from their participation in clinical trials during the development of liraglutide.

The three other named health professionals were not approached by Novo Nordisk and were not asked to participate in any launch activities for liraglutide.

Novo Nordisk submitted that therefore, Lilly's allegation that 'the remarkable consistency of the messaging supporting liraglutide' was based on inaccurate and misleading media and speaker briefing by Novo Nordisk was unfounded.

Novo Nordisk provided copies of the Media Backgrounder Package which consisted of seven separate documents 'Changing Diabetes' (ref UK/LR/0509/0143), 'Diabetes Facts' (ref UK/LR/0509/0144), 'Diabetes Information' (ref UK/LR/0509/0145), 'Incretins' (ref UK/LR/0509/0146), 'Facts about type 2 Diabetes Treatment' (ref UK/LR/0509/0147), 'Novo Nordisk - the Diabetes Care Company' (ref UK/LR/0509/0148) and 'Victoza (liraglutide)' (ref UK/LR/0509/0149). These were to be distributed within the press pack. The speaker briefing pack for the Victoza media launch included details of the launch schedule for Novo Nordisk's three speakers. One of the speakers gave a presentation 'Changing Times, Changing Diabetes'. Another speaker presented on the patient perspective and was to give interviews including on 8 July on 'This morning' and be available for more interviews. Speakers were available to answer questions either in front of the whole audience or on an individual basis. The brief for a third speaker referred to radio interviews to be held on 7 July 2009.

Novo Nordisk had issued two press releases, one for the medical press and one for the lay press. Both press releases included a section headed 'Additional benefits' these being weight loss, reduction in systolic blood pressure and improved beta-cell function.

1 Article in the Mail Online 'The once-a-day diabetes jab that fights obesity'

COMPLAINT

Lilly alleged that the title and content of the article clearly invited the lay reader to consider that liraglutide was primarily an anti-obesity treatment in patients who happened to have type 2 diabetes. Readers were not told that the main measure of liraglutide's effectiveness was the establishment of adequate blood sugar control as measured by reductions in glycosylated haemoglobin (HbA1c) after six months or one year. Whilst a balanced and appropriately focused discussion of obesity as a risk factor associated with type 2 diabetes was reasonable, this article focussed almost entirely on the 'obesity time-bomb' which underlay the implicit message that this could be averted by treatment with liraglutide. The reader was led to believe that managing obesity with liraglutide was the primary therapeutic goal and by preventing this, type 2 diabetes and its complications could be avoided or improved. The licensed indication of liraglutide, to achieve glycaemic control in combination with other antidiabetic agents, was relegated almost to an anecdote in the body of the article where again, by its direct association with the numerous claims promoting the weight reducing benefits of liraglutide, this critical information was effectively buried thus ensuring that the precise indication of liraglutide remained ambiguous. Given the absence of the qualification that liraglutide should be used in combination with other antidiabetic agents, it was implied that liraglutide could be used as monotherapy. This misleading impression was further enhanced by the repeated and unqualified emphasis on the once-daily dosing which suggested to the lay reader that all that type 2 diabetics needed to manage their condition was a treatment regimen that only involved once-daily dosing with liraglutide.

The discussion of the weight reduction benefit associated with liraglutide was often couched by an off-licence statement such as 'A new diabetes jab could help fight obesity caused by insulin intake' and 'Experts say that the injection, called Victoza, could help prevent thousands of type 2 diabetes suffers having to take insulin – which can cause weight gain'. These statements were misleading and disparaged insulin. To single out insulin in this regard was unbalanced given that sulphonylureas were also associated with weight gain. The alarmist language adopted to discuss the risk of obesity and weight gain associated with insulin was of concern given that many readers would be insulin-dependent type 2 diabetics for whom liraglutide was not an option. Further, the assertion that liraglutide could help type 2 diabetics from becoming insulin-dependent or '… help sufferers to stay off insulin' was misleading, unsubstantiated and raised unfounded hopes and expectations of successful treatment with liraglutide in breach of Clauses 7.2, 7.3, 7.4 and 8.1 of the Code.

Similarly, statements such as 'Another benefit is that it lowers blood pressure, which is a factor in heart disease' and quotations attributed to a Novo Nordisk spokeswomen, such as '… this treatment has a positive effect on blood pressure levels' were intended to lead the lay reader to infer that liraglutide was also licensed to treat '… high blood pressure levels' and, by association, complications such as heart disease. The latter information was an unqualified generalisation, misleading and could not be substantiated. It should, more accurately, refer to systolic blood pressure, clarify and qualify

the statistical and clinical significance of any blood pressure reduction with respect to particular dosages of liraglutide. Notwithstanding the omission of the latter, Lilly questioned the relevance of this information to a lay audience. The prominence that this was given was clearly aimed at promoting the additional unlicensed benefits of liraglutide to the public. The reference to and emphasis on these other attributes of liraglutide, other than its effect on glycaemic control, was inconsistent with the liraglutide SPC and therefore in breach of Clause 3.2.

The overwhelming emphasis on the weight reduction benefit of liraglutide was likely to raise unfounded hopes of successful treatment with regard to the sustained and long-term reduction in weight loss associated with liraglutide; no data was currently available to substantiate any such suggestion. The same could be said of the implied claim that liraglutide offered protection against heart disease by virtue of its unqualified effect on blood pressure; this was a breach of Clauses 7.2, 7.3, 7.4 and 7.10.

The promotional nature of the article was evidenced by four separate mentions of Victoza, which went beyond the purpose of identification; numerous statements such as 'Victory for Victoza?' and 'Scientists have developed a revolutionary once-a-day injection that controls the symptoms of diabetes and helps fights obesity' read like advertising copy. This was a breach of Clauses 12.1, 22.1, 22.2 and 22.5. The advertising of liraglutide to the public was further emphasised by similarly sensationalist quotations attributed to a Novo Nordisk spokesman such as 'It could herald a new age in diabetes treatment'. The latter clearly exaggerated the facts given that liraglutide was the second GLP-1 analogue to be marketed. The quotation attributed to another Novo Nordisk spokesman that 'This is an important advance for patients with type 2 diabetes, many of who are already overweight' again invited consideration of the weight reduction benefit of liraglutide but critically, also implied that products such as metformin and the first GLP-1 analogue, Byetta, offered no such benefit or advance in this regard. Similarly, statements that '…[liraglutide] also reduces weight - which is extraordinarily good news' again implied that products such as Byetta offered no additional weight loss benefit and were consequently entirely ordinary; this was not the case given that metformin was the initial treatment of choice for many overweight, newly diagnosed type 2 diabetics. A breach of Clauses 7.2 and 8.1 was alleged.

The misleading and promotional nature of the Novo Nordisk briefing materials was evidenced by the statement that '… the jab will soon be available free on the NHS'. This suggested that prescribing information was included in the briefing materials, contrary to the Code and implied that other antidiabetic treatments were not available free on the NHS.

Given the intended audience, none of the Novo Nordisk spokespersons referred to the safety and tolerability of liraglutide particularly with regard to the incidence of gastrointestinal side effects, which occurred very commonly, and hypoglycaemia which occurred commonly or very commonly when it was used in combination with glimepiride, metformin and glimepiride or metformin and rosiglitazone. This was an important omission when considered alongside the copious discussion promoting the benefits of liraglutide; one which was likely to mislead the reader about the potential risks associated with it. This was a breach of Clauses 7.2, 7.9 and 7.10.

RESPONSE

Novo Nordisk refuted the allegation that the quotations in the Daily Mail article were based on Novo Nordisk speaker briefings. Two of the three health professionals referred to in the article had never been contacted by Novo Nordisk in relation to liraglutide, and thus the quotations reflected their own independent professional opinions. Although the third quotation was by a physician who Novo Nordisk had asked to provide his own professional and independent opinion about liraglutide, his statement was fully aligned with the Victoza SPC which stated that 'Liraglutide reduces body weight and body fat mass through mechanisms involving reduced hunger and lowered energy intake'. Further he did not suggest that a primary indication of Victoza was weight reduction ('With Victoza, patients with type 2 diabetes can be confident they are controlling their blood sugar and **may** benefit from weight loss. This is an important advance for patients with type 2 diabetes, many of whom are already overweight' (emphasis added)).

The media backgrounder press packs provided by Novo Nordisk contained information about diabetes, the company and liraglutide. The material clearly stated that liraglutide was indicated for the treatment of type 2 diabetes in combination with metformin or sulphonylurea and in combination with metformin plus sulphonylurea or metformin plus thiazolidinedione. The potential weight sparing and blood pressure lowering features of liraglutide were highlighted, in accordance with the SPC as additional and relevant benefits of the medicine. As such, the press packs provided a comprehensive and accurate clinical perspective, in line with the SPC. The briefing material did not suggest that liraglutide was licensed to treat obesity and hypertension, and if, as alleged by Lilly this impression had been given by the journalists, this was not in response to information provided by Novo Nordisk.

Further, Novo Nordisk did not have any editorial control as to the content of the interviews and articles, and did not believe it could be held responsible for the way in which the journalists chose (in their absolute discretion) to report Victoza, nor could it be held responsible for the fact that the article did not mention Byetta and its weight

reducing benefits and the fact that Victoza must be used in combination with specific oral antidiabetic medicines, and nor did Novo Nordisk believe that the likely interpretation and assumption taken from this article was that liraglutide was the only treatment for type 2 diabetes which could provide long-term weight loss and cardiovascular protection, given the omission of the mention of other agents, such as Byetta.

The emphasis made by the journalist that insulin treatment was associated with weight gain in the majority of patients, and treatment with liraglutide could lead to weight loss was widely accepted by health professionals.

Novo Nordisk denied any breach of the Code.

PANEL RULING

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself. Clause 22.1 prohibited the advertising of prescription only medicines to the general public. Clause 22.2 permitted information about prescription only medicines to be supplied directly or indirectly to the general public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific prescription only medicine. Lilly had not seen Novo Nordisk's materials. Its complaint was based on press articles.

The Panel noted that Novo Nordisk had not specifically confirmed whether the journalist from the Daily Mail had attended the press launch or whether an additional interview was arranged for him as part of the media activity referred to in the speakers' briefing. The article at issue quoted three health professionals. One of whom was reported as stating 'With Victoza patients with Type 2 diabetes can be confident they are controlling their blood sugar and may benefit from weight loss'. The Panel noted that this quotation was included in the medical and lay press releases issued by Novo Nordisk.

The Panel considered the question of Novo Nordisk's responsibility under the Code for comments made by health professionals. It was clear that Novo Nordisk was responsible for the quotations included in its press pack. The Panel noted that Novo Nordisk had involved three health professionals with the launch who were briefed by Novo Nordisk which had facilitated their availability for interviews. The Panel decided that Novo Nordisk was responsible under the Code for comments made by the three health professionals. Companies could not use independent experts as a means of avoiding the restrictions in the Code.

Novo Nordisk was not responsible for the content of the article in the Daily Mail per se. The Panel would consider Lilly's allegations in relation to Novo Nordisk's press materials which had not been seen by Lilly. The Panel considered that each individual piece had to be capable of standing alone with regard to the requirements of the Code. An otherwise misleading statement in one backgrounder or press release could not be qualified by statements in other material. The Panel examined the Media Backgrounder Package and the two press releases.

The Media Backgrounder Package consisted of seven documents 'Changing Diabetes', 'Diabetes Facts', 'Diabetes Information', 'Incretins', 'Facts about type 2 Diabetes Treatment', 'Novo Nordisk – the Diabetes Care Company' and 'Victoza (liraglutide)'.

The backgrounder 'Facts about type 2 Diabetes Treatment' included a number of sections, firstly 'Lowering blood glucose' which was followed by a section 'Beyond blood glucose' which gave information about obesity, high blood pressure and elevated cholesterol.

The backgrounder 'Incretins' mentioned GLP-1 and Victoza. It was not clearly stated that Victoza was indicated in combination with metformin and/or a sulphonylurea or metformin and a thiazolidinedione. Victoza was not indicated for first line use or as monotherapy. In a section headed 'Victoza (liraglutide)' this backgrounder referred to liraglutide lowering glucose levels by stimulating insulin release when glucose levels became too high. It also stated that liraglutide's impact on HbA1c control, weight loss, reduction in systolic blood pressure and improved beta-cell function had been consistently demonstrated throughout the phase 3a Liraglutide Effect and Action in Diabetes (LEAD) trials. The document referred to the European Medicines Evaluation Agency's (EMEA's) positive opinion 'recommending a marketing authorisation for the treatment of type 2 diabetes'.

Immediately below the heading of the 'Victoza (liraglutide)' backgrounder the indication for the product was stated followed by a section 'The importance of type 2 diabetes risk factors' which stated that addressing risk factors for cardiovascular disease, including HbA1c, body weight and blood pressure was key to managing type 2 diabetes. It included similar statements regarding Victoza's mechanism of action to those in the 'Incretin' backgrounder. Quantative data was provided about the results of clinical studies (LEAD 1, LEAD 2 and LEAD 4) with regard to HbA1c reduction, weight loss, hypoglycaemia incidence, systolic blood pressure and cholesterol levels. A further open label study comparing liraglutide with exenatide was mentioned (LEAD 6). Detailed data was included.

The medical press release and lay press releases bore the same reference number. Both featured boxed text on the first page which stated the

indications for Victoza.

Both press releases stated under a section headed 'Additional benefits' that Victoza could help patients achieve weight loss by increased satiety and delayed gastric emptying, and thus reduced calorie intake. This was referred to as an important factor in treating type 2 diabetics as many were overweight. This section also referred to reduced systolic blood pressure and improved beta-cell function. The quotation 'With Victoza, patients with type 2 diabetes can be confident they are controlling their blood sugar, and may benefit from weight loss. This is an important advance for patients with type 2 diabetes, many of whom are already overweight' was also included. A similar section appeared in the lay press release. The medical press release included a section on comparative studies.

The lay press release included statements 'Victoza is the first once-daily human Glucagon-like peptide-1 (GLP-1) analogue', 'Victoza lowers blood sugar levels by stimulating the release of insulin only when glucose levels become too high' and 'Victoza is a convenient once-daily injection that can be taken any time of day, irrespective of meals' which appeared immediately beneath the heading 'Novo Nordisk launches Victoza (liraglutide) in the UK, a new once-daily treatment for type 2 diabetes'.

The Panel noted that none of the press pack (the press releases and relevant backgrounders) included details of precautions for use or side effects of Victoza. This was likely to mislead regarding the overall benefits of the product as alleged. Breaches of Clauses 7.2, 7.9 and 7.10 were ruled with regard to the materials for the press.

The Panel was concerned that the overall impression of the press pack was that Victoza was to be prescribed to control blood glucose, reduce weight, reduce blood pressure and improve beta-cell function. The materials were not clear regarding the licensed indication as set out in Section 4.1 of the SPC. The materials placed equal emphasis on the information set out in Section 5.1 of the SPC with regard to reductions in weight and blood pressure and improved beta-cell function. Readers might be confused as to the precise indication for Victoza. Little mention was made that the product was only to be prescribed as combination therapy when first and/or second line oral treatment options had failed to produce adequate glycaemic control.

The Panel noted that according to the SPC weight loss from baseline ranged from 2.79kg to 0.23kg for patients taking 1.8mg liraglutide in combination with metformin or glimepiride respectively. For patients on 1.2mg liraglutide plus metformin weight loss was 2.58kg whilst those who were treated with 1.2mg liraglutide plus glimepiride gained 0.32kg. The change in baseline for patients not taking liraglutide ranged from -1.51kg to +2.11kg.

The Panel questioned whether the emphasis on weight reduction in the press pack was supported by the data. Marre *et al* (2009) (LEAD 1) compared the effects of combining liraglutide or rosiglitazone or placebo with glimepiride. Mean reductions in weight from baseline were 0.2kg with liraglutide 1.8mg and 0.1kg with placebo. Increases occurred with liraglutide 1.2mg (0.3kg) or rosiglitazone (2.1kg). Unlike rosiglitazone weight did not increase substantially with liraglutide and the differences between rosiglitazone and liraglutide were statistically significant (-2.3 to -1.4kg $p<0.0001$) although there were no significant differences compared to placebo.

The study authors listed the short duration (26 weeks) as a limitation of the trial. Zinman *et al* (July 2009) (LEAD 4) showed statistically significant greater weight loss in the liraglutide groups compared with the placebo group ($p<0.0001$) (added to a regimen of metformin and rosiglitazone). The weight loss in the 1.8mg liraglutide group (2 ± 0.3kg) was statistically significantly different to the weight loss in the 1.2mg liraglutide group (1 ± 0.3kg) ($p=0.011$).

Buse *et al* (2009) (LEAD 6) compared the addition of liraglutide 1.8mg once daily or exenatide 10mcg twice daily to patients inadequately controlled on maximally tolerated doses of metformin, sulphonylurea or both. Differences between the products were noted. However, the mean weight reduction for liraglutide (3.24kg) and for exenatide (2.87kg) were similar and similar proportions of patients lost weight, 78% with liraglutide compared to 76% with exenatide.

The Panel noted that the data was based on mean body weight for a group of patients but this was not made clear in the press pack. The impression was given that every patient taking liraglutide would lose weight and this was not so. Buse *et al* (LEAD 6) showed that 22% of patients lost no weight. No information was given about this group of patients; some might have gained weight.

The Panel considered that the statement in the backgrounders 'Incretins' and 'Victoza (liraglutide)' which referred equally to Victoza's impact on HbA1c control, weight loss, reduction in systolic blood pressure and improved beta-cell function being consistently demonstrated in clinical trials were misleading with regard to the licensed indication for Victoza and inconsistent with the SPC. It appeared that Victoza could be prescribed as much for its additional benefits as its licensed indication ie glycaemic control. A breach of Clause 3.2 was ruled. This ruling was appealed.

The Panel noted that Novo Nordisk in its response had referred to the potential 'weight sparing' feature of liraglutide. This phrase was not used in the press materials. The Panel considered that the emphasis in the backgrounder documents on weight reduction was misleading. The available data was for no longer than 26 weeks and related only to certain combinations of liraglutide and oral antidiabetic agents. The weight reduction had not

been quantified in the 'Incretins' backgrounder and in the Panel's view this was very important. The SPC clearly stated that the reduction ranged between 1kg and 2.8kg. Given the association between type 2 diabetes and excess body weight it was important that the magnitude of potential weight loss was made clear. Even with the weight loss reported with Victoza, most patients in the LEAD studies were likely to remain overweight if not obese (BMI>30). The data was less positive for the 1.2mg Victoza dose in that mean bodyweight increased by 0.23kg in the 1.2mg liraglutide and glimepiride group. The Panel considered that the 'Incretins' backgrounder was misleading in this regard and not capable of substantiation. Breaches of Clauses 7.2 (not appealed) and 7.4 (this ruling was appealed) were ruled. It was also exaggerated and a breach of Clause 7.10 was ruled. There was no comparison in the 'Incretins' backgrounder and thus no breach of Clause 7.3 was ruled.

With regard to the backgrounder 'Victoza' (liraglutide) the Panel noted that some of the weight change data (increases and reduction) had been quantified. However the impression was given that all patients on a Victoza combination would lose weight and that was not so. The SPC data showing weight gain for liraglutide 1.2mg was not included. The Panel considered that although detailed data was presented this was not comprehensive. The backgrounder 'Victoza (liraglutide)' was misleading as it did not reflect the totality or limitations of the data and was not capable of substantiation. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled. The backgrounder was exaggerated and a breach of Clause 7.10 was ruled. These rulings were appealed.

The Panel noted its ruling of a breach of Clauses 7.2, 7.9 and 7.10 in relation to a general allegation regarding the absence of information about precautions for use or side effects. The Panel was concerned that neither of the backgrounders 'Incretins' and 'Victoza (liraglutide)' referred to side effects and contraindications for the product. Neither was it sufficiently clear that the product was to be used second or third line and in combination with oral antidiabetics. The Panel considered that the backgrounders were not presented in a balanced way and would raise unfounded hopes of successful treatment. A breach of Clauses 7.2 and 22.2 was ruled. The Panel did not consider the backgrounders were promotional material as such. They were not disguised promotion and no breach of Clauses 12.1 and 22.1 was ruled.

With regard to statements about blood pressure the Panel noted that the backgrounders referred to reductions in systolic blood pressure. Section 5.1 of the SPC stated that Victoza decreased systolic blood pressure by an average of 2.3 to 6.7mmHg from baseline and compared to active comparator the decrease was 1.9 to 4.5mmHg. The available data was for no longer than 26 weeks and related only to certain combinations of liraglutide and oral antidiabetic agents. Marre *et al* (LEAD 1) stated that the decreases in systolic blood pressure with Victoza 1.2 mg or 1.8mg combined with glimepiride (2.6 – 2.8Hg) were not statistically significantly different from placebo or rosiglitazone combined with glimepiride (0.9 – 2.3mmHg).

Nauck *et al* (2009) (LEAD 2) stated that the treatment differences compared with glimepiride plus metformin were statistically significant (1.2mg Victoza plus metformin reduction of 3.2mmHg, p=0.0128 and 1.8mg Victoza plus metformin reduction of 2.7mmHg, p=0.0467).

Zinman *et al* (LEAD 4) stated that the 1.2 and 1.8mg liraglutide groups (in combination with metformin plus rosiglitazone) had statistically significant reductions in mean systolic blood pressure compared with the placebo group (placebo corrected difference 1.2mg Victoza combination reduction of 5.6mmHg p<0.0001 and 1.8mg Victoza combination reduction of 4.5mmHg p=0.0009).

Russell-Jones *et al* (2009) (LEAD 5) stated that the difference between 1.8mg Victoza in combination with metformin plus glimepiride, reduction of 4mmHg and placebo was not statistically significant.

Buse *et al* (LEAD 6) stated that systolic blood pressure for 1.8mg liraglutide (plus metformin or sulphonylurea or both) was reduced by 2.51mmHg.

The 'Incretins' backgrounder stated that liraglutide's impact on, *inter alia*, reduction in systolic blood pressure had been consistently demonstrated throughout the phase 3a LEAD trials. The reduction was not quantified and nor was any benefit claimed for the reduction. There was no claim implied or otherwise regarding protection against heart disease as alleged and thus no breach of Clauses 7.2, 7.3, 7.4 and 7.10 was ruled.

The 'Victoza liraglutide' backgrounder stated that addressing risk factors for cardiovascular disease was one of a number of risk factors key to managing diabetes. Liraglutide's impact on, *inter alia*, reduction in systolic blood pressure had been consistently demonstrated throughout the phase 3a LEAD trials. The data from Marre *et al* (LEAD 1), Nauck *et al* (LEAD 2) and Buse *et al* (LEAD 6) were not quantified. The data from Zinman *et al* (LEAD 4) was quantified but did not give the placebo corrected differences. The Panel did not consider that the backgrounder implied a claim for protection against heart disease as alleged and thus no breach of Clauses 7.2, 7.3, 7.4 and 7.10 was ruled.

The Panel did not consider that the backgrounders 'Incretins' and 'Victoza (liraglutide)' disparaged insulin treatment. Insulin was only mentioned in relation to the effect of naturally occurring insulin rather than treatment with it. There was no mention of Victoza helping patients stay off insulin. The Panel ruled no breach of Clauses 7.2, 7.3, 7.4 and 8.1.

The backgrounder 'Diabetes treatment' referred to

insulin becoming the preferred option when tablets were not enough to manage type 2 diabetes. A similar statement appeared in the backgrounder 'Facts about type 2 Diabetes Treatment'. The Panel did not consider that these two backgrounders disparaged insulin treatment as alleged. There was no statement to the effect that Victoza helped patients stay off insulin. The Panel ruled no breach of Clauses 7.2, 7.3, 7.4 and 8.1.
Turning to the speaker briefing pack the Panel did not consider that the contents were unacceptable as alleged. The material was primarily about the logistics for the launch event and other activities. The launch was described as being key to raising awareness about Victoza; it would increase understanding of the product and the benefits to patients and physicians. The Panel considered it was surprising that no information about Victoza was provided to the speakers. Nor was any information or guidance given about compliance with the Code. The Panel considered that Lilly's allegations about the speaker briefing pack were addressed by the Panel's rulings about the other press materials. It thus decided not to make any rulings about the speaker briefing pack.

With regard to the press releases the Panel was concerned that they were wholly positive about the product. None of the side effects or contraindications had been included. The use of Victoza in combination with oral antidiabetic medicines and that it would be used in effect second or third line when oral antidiabetic therapy was not tolerated or glycaemic control was insufficient despite dual therapy was not made clear. With regard to possible weight loss the press releases did not quantify the amount and the Panel considered that this was very important. Clinicians and patients might be misled by the very positive but undetailed weight reduction claims. The Panel considered that the data regarding weight loss in both the lay press release and the medical press release were misleading and not capable of substantiation. Breaches of Clauses 7.2 (not appealed) and 7.3 and 7.4 (both appealed) were ruled. The press releases exaggerated the position and a breach of Clause 7.10 was ruled. The Panel considered that the health professional's claim that '… patients with type 2 diabetes can be confident they are controlling their blood sugar, and may benefit from weight loss. This is an important advance for patients with type 2 diabetes, many of whom are already overweight' implied that if patients on liraglutide lost weight the amount lost meant that they would no longer be overweight. This was not so. Breaches of Clauses 7.2, 7.3 and 7.10 were ruled. A ruling of a breach of Clause 7.4 was appealed. The Panel considered that the quotation was misleading in referring to Victoza being an important advance with regard to the potential weight loss benefit. The data for Byetta, Buse *et al*, LEAD 6, demonstrated a similar weight loss for both products and both were licensed for glycaemic control. A breach of Clause 7.2 was ruled. The Panel, however, did not consider that the claim disparaged Byetta and thus no breach of Clause 8.1 was ruled.

The Panel did not consider that the references to the benefit of a reduction of systolic blood pressure in either press release were unacceptable; no benefit for the reduction was claimed or implied. No breach of Clauses 7.2, 7.2, 7.4 and 7.10 was ruled.

The Panel considered that the press releases were inconsistent with the SPC and were misleading with regard to the licensed indication. Breaches of Clauses 3.2 and 7.2 were ruled. These rulings were appealed.

The Panel considered that the inclusion of the very positive claims in the lay press release and the lack of information about side effects etc in effect turned the lay press release into an advertisement for a prescription only medicine and a breach of Clause 22.1 was ruled which was appealed.

The Panel considered that neither press release presented the information in a factual balanced way. The press releases would raise unfounded hopes of successful treatment particularly with regard to weight loss. Statements had been made in the lay press release to encourage the public to ask their health professional for Victoza. Each was ruled in breach of Clause 22.2.

The material was not clear that patients with type 2 diabetes using insulin could not be given Victoza. However, the Panel did not consider that the press releases disparaged insulin treatment. Insulin was only mentioned in relation to the effect of naturally occurring insulin rather than treatment with it. There was no mention of Victoza helping patients stay off insulin. The Panel ruled no breach of Clauses 7.2, 7.3, 7.4 and 8.1.

The Panel ruled no breach of Clause 22.5 which required that companies were responsible for information about products issued by their public relations agency. This was a statement of principle and not a requirement that could be breached.

APPEAL BY NOVO NORDISK

Novo Nordisk emphasized its general concern about the significant discrepancies between the Panel's rulings and the MHRA pre-vetting approvals and noted that the following Victoza launch materials, ruled in breach of the Code by the Panel, had been pre-vetted by the MHRA:

1 all the media backgrounders referred to;
2 the press releases;
3 the journal advertisement;
4 the reprint folders;
5 the leavepieces; and
6 the website.

The patient support booklet and the Formulary Pack were not pre-vetted by the MHRA, as they were issued after receipt of the letter of 29 June 2009 in which the MHRA stated that it no longer needed to pre-vet Novo Nordisk's promotional materials. The normal period for pre-vetting was up to six months

and the Blue Guide stated that 'this time period may be reduced or extended depending on the quality of the initial advertising material submitted and other relevant factors'. Novo Nordisk noted that the MHRA's pre-vetting of Victoza continued for just one month.

Novo Nordisk noted that the Memorandum of Understanding between the ABPI and MHRA of November 2005 confirmed the importance of co-operation between the MHRA and PMCPA 'to promote efficient complaint procedures without compromising the independence of each party'. The company further appreciated that 'The ABPI Code covers and extends beyond the UK law and it is thus possible that material pre-vetted and approved by the MHRA might subsequently be ruled to be in breach of the ABPI Code' and that 'Material subject to the ABPI Code considered by the MHRA as being potentially in breach of UK regulations, is very likely also to be in breach of the ABPI Code'.

However, Novo Nordisk submitted that the converse was likely to be true in that materials approved against statutory provisions (ie the Medicines Act 1968, the Medicines (Advertising) Regulations 1994/3144 ('Advertising Regulations') and the other delegated legislation made under the Act, and the MHRA Blue Guide) under the MHRA pre-vetting procedure should not subsequently be held to be in breach of equivalent provisions of the Code. Whilst the respective roles of the two bodies as envisaged in the Memorandum of Understanding might differ, it seemed wholly inappropriate for the decision of the MHRA fulfilling its statutory role to be later 'overruled' by the PMCPA.

Specifically Novo Nordisk submitted that: Clause 3.2 of the Code was directly reflected by Regulation 3A (1) of the Advertising Regulations; and Clauses 7.2, the requirement in Clause 7.3 that promotion must not be misleading and Clause 7.4 of the Code were to a material extent matched by the provisions of Regulation 3A (2) and (3) of the Advertising Regulations and Paragraph 4.3 of the Blue Guide. Clause 22.1 of the Code mirrored Paragraph 5.2 of the Blue Guide which related to Regulation 7 of the Advertising Regulations.

Novo Nordisk submitted that as the effect and intent of these respective provisions were effectively identical the apparent inconsistency in interpretation as between the MHRA and PMCPA was therefore difficult to understand. Novo Nordisk further submitted that with respect to all of the alleged breaches below in relation to materials previously pre-vetted by the MHRA, those based on Clauses 3.2 and 22.1 (and to a substantial degree Clauses 7.2 and 7.4) as ruled by the Panel should not be upheld.

Novo Nordisk submitted that against this background it was understandably concerned and surprised about the two breaches of Clause 2 that had been ruled where the substance of the breaches were Clauses 3.2 and 22.1, particularly given that the MHRA was evidently very satisfied with the quality of the materials (shown by the unusually short pre-vetting period).

Novo Nordisk submitted that such significant discrepancies between the MHRA and the PMCPA harmed the industry and were contrary to the spirit of the Memorandum of Understanding.

Media Backgrounder Package/Press Releases

Novo Nordisk agreed that complaints should be judged on the information provided by Novo Nordisk rather than the content of any articles and so it confined its arguments and remarks to the content of the media backgrounder package and the press releases. However, Novo Nordisk challenged the Panel's decision that each part of the package should be considered wholly in isolation. The media backgrounder package should be scrutinized in its entirety as it was provided to journalists as a complete pack containing the relevant press release (medical media or lay press) and the backgrounders. The press would have been fully aware of the licensed indication of Victoza, as it was clearly highlighted at the beginning of the press releases and was placed on the product-specific backgrounder ('Victoza (liraglutide)').

As these materials were prepared for the launch of Victoza, Novo Nordisk was no longer using the press releases and media backgrounder package that were the subject of these rulings.

Novo Nordisk noted that the Panel considered that inappropriate significance was given to additional benefits as opposed to licensed indications. Novo Nordisk submitted that proper emphasis was placed on Victoza's licensed indication in the backgrounders. The 'Victoza (liraglutide)' backgrounder clearly stated the licensed indication immediately between the title and the heading immediately below ('The importance of type 2 diabetes risk factors'). Thus, in the Victoza (liraglutide) backgrounder, the references to the impact of liraglutide on weight loss, reduction in systolic blood pressure and improved beta-cell function – the additional benefits – (in the first and fourth paragraphs of page 1) immediately followed the statements as to the licensed indication. Similarly, in the 'Incretins' backgrounder under the heading 'Victoza (liraglutide)' it was clearly stated initially that 'Liraglutide is a once-daily human GLP-1 analogue. Liraglutide lowers glucose levels by stimulating the release of insulin only when glucose levels become too high'. Only in the immediately following sentence was there reference to 'weight loss, reduction in systolic blood pressure (SBP) and improved beta cell function'. In addition, the media backgrounder package of which this backgrounder was a part, should be read as a whole.

Novo Nordisk submitted that it was inappropriate and unjust for the Panel to rule a breach of Clause 3.2 of the Code when the same item was approved

by the MHRA as being in compliance with Regulation 3A(1) of the Advertising Regulations and Paragraph 4.3 of the Blue Guide. Therefore Novo Nordisk denied that the media backgrounder package as a whole and the Incretins' and 'Victoza (liraglutide)' backgrounders were in breach of Clause 3.2.

Novo Nordisk noted that the Panel considered that the weight claims in the 'Incretins' backgrounders could not be substantiated because the weight finding related only to certain combinations of liraglutide and oral antidiabetic agents, the weight loss data was not quantified and the majority of patients was likely to remain overweight/obese after the weight loss.

Section 5.1 of the Victoza SPC stated that liraglutide in combination with metformin, metformin and glimepiride and metformin and rosiglitazone was associated with sustained weight reduction of 1.0 to 2.8kg. These combinations covered three out of four potential licensed combinations. The only combination in which liraglutide was revealed to be weight neutral (0.23kg weight loss with 1.8mg and 0.32kg weight gain with 1.2mg) was the combination with glimepiride. Even in this latter combination the use of liraglutide was not associated with clinically significant weight gain. Although the 0.32kg weight gain on the 1.2mg arm was statistically significantly different compared with placebo (-0.1kg), this difference could hardly be considered as clinically relevant.

Novo Nordisk noted that in the LEAD trials liraglutide was investigated in eight study arms and in seven either 1.8mg or 1.2mg was associated with statistically significant weight loss Marre *et al* (LEAD 1), Nauck *et al* (LEAD 2), Zinman *et al* (LEAD 4) and Russell-Jones *et al* (LEAD 5), 2009. Novo Nordisk believed that on the basis of this evidence the overall claim of 'weight loss' was justified and appropriate.

As to the Panel's concern as to quantification of weight loss, Novo Nordisk submitted that the quantification of the observed weight losses with liraglutide throughout the LEAD trials which the Panel remarked was missing from the 'Incretins' backgrounder, could be found in the product related backgrounder of 'Victoza (liraglutide)'. It was inappropriate to rigidly consider each backgrounder within the media backgrounder package in isolation, as they were all provided together as a single pack.

Novo Nordisk submitted that clinically no medicine would be expected to normalize the patient's body weight in order to make a favourable weight claim. Such an impact was not even required by the regulatory authorities to support an antiobesity indication.

Novo Nordisk noted that whilst Clauses 7.2 and 7.4 of the Code and Regulations 3A(2) and (3) of the Advertising Regulations/Paragraph 4.3 of the Blue guide were not entirely equivalent, pre-vetting against such requirements took place.

On the basis of the above, Novo Nordisk therefore disagreed with the Panel that the weight claim in the 'Incretins' Backgrounder could not be substantiated and was therefore in breach of Clause 7.4 of the Code.

Novo Nordisk noted that the Panel had considered that the 'Victoza (liraglutide)' backgrounder implied that all patients using Victoza lost weight and alleged that the weight gain data relating to the 1.2mg dose as evidenced by the SPC was not shown. Novo Nordisk submitted that it did not understand the Panel's objection here as the 'Victoza (liraglutide)' backgrounder clearly stated in relation to Marre *et al* (LEAD 1) at paragraph 5 on page 2 that: 'Changes in body weight with liraglutide 1.2mg (+0.3kg, baseline 80kg) were less than with rosiglitazone (+2.1kg, $p<0.001$, baseline 80.6kg)'. The balance of medical evidence was sufficient enough to make a favourable weight claim, as discussed above.

Novo Nordisk therefore disagreed with the Panel that the 'Victoza (liraglutide)' backgrounder was in breach of Clauses 7.2, 7.3, 7.4 and 7.10 of the Code.

Novo Nordisk noted that the Panel considered that the data regarding weight loss in both the press releases were not capable of substantiation, and therefore in breach of Clause 7.4 of the Code. The Panel also ruled a breach of Clause 7.3.

With respect to the breach of Clause 7.4 Novo Nordisk reiterated its comments in relation to the above, indicating that the overall medical evidence substantiated the weight loss claim in relation to liraglutide. Whilst Clauses 7.2 and 7.4 of the Code and Regulations 3A(2) and (3) of the Advertising Regulations/Paragraph 4.3 of the Blue Guide were not entirely equivalent, Novo Nordisk noted that pre-vetting against such requirements took place. As to the ruling of a breach of Clause 7.3, in that it related to comparisons, Novo Nordisk did not understand its relevance and appealed on that basis.

Novo Nordisk noted that the Panel was concerned that the quotation from Professor Barnett ('… may benefit from weight loss') implied that patients would lose weight with liraglutide resulting in being no longer obese/overweight, and was therefore unsubstantiated. Novo Nordisk strongly disagreed with this interpretation. Making a favourable weight claim about a compound did not mean that all patients using the medicine would, in fact, lose weight, or, indeed, that the weight loss would be sufficient to make them no longer obese/overweight. This was not a realistic clinical expectation. Furthermore, as noted above, interpreting such a claim as a statement to the effect that patients would no longer be overweight/obese was inappropriate. No health professionals would reasonably expect such an impact. A better and more realistic view was that the above wording (particularly use of the word

'may') would simply be interpreted as meaning that some patients would lose weight. As explained above, this claim could be substantiated and Novo Nordisk therefore reiterated its arguments in that respect.

Novo Nordisk submitted that, whilst Clauses 7.2 and 7.4 of the Code and Regulations 3A(2) and (3) of the Advertising Regulations/Paragraph 4.3 of the Blue Guide were not entirely equivalent, it noted that pre-vetting against such requirements took place. Therefore, Novo Nordisk disagreed with the Panel that using the quote from the health professional in the press releases was in breach of Clause 7.4 of the Code.

Novo Nordisk noted that the Panel considered the press releases misleading and inconsistent with the Victoza SPC with regard to the licensed indication. Novo Nordisk submitted that it did not understand how the press releases could be misleading by implying unlicensed indications for liraglutide since there were prominently highlighted boxes clearly specifying the licensed indication immediately under the headline of both items. Furthermore the press releases went onto describe the mechanism by which liraglutide reduced blood glucose levels (the licensed indication) and only referred in the paragraph below under the sub-heading 'Addition benefits' to the observed weight loss, systolic blood pressure reduction and beta-cell function improvement as additional benefits of liraglutide.

Novo Nordisk argued that it was inappropriate and unjust for the Panel to rule a breach of Clause 3.2 of the Code when the same item was approved by the MHRA as being in compliance with Regulations 3A(1) of the Advertising Regulations and Paragraph 4.3 of the Blue Guide. In addition, whilst Clauses 7.2 and 7.4 of the Code and Regulations 3A(2) and (3) of the Advertising Regulations/Paragraph 4.3 of the Blue Guide were not entirely equivalent, Novo Nordisk noted that pre-vetting against such requirements took place. Thus on the basis of the above and the previously detailed arguments related to the Media Backgrounder Package, Novo Nordisk disagreed with the Panel that the press releases were in breach of Clauses 3.2 and 7.2 of the Code.

Novo Nordisk submitted that it was inappropriate and unjust for the Panel to rule a breach of Clause 22.1 of the Code when the MHRA had considered that the same item complied with, *inter alia*, Paragraph 5.2 of the Blue Guide.

COMMENTS FROM LILLY

Lilly submitted that Novo Nordisk was unreasonable to assert that each part of the package should not be considered in isolation by the Code. This presupposed that all journalists would necessarily and diligently scrutinize the entire content of the media backgrounder package and not simply elect to read what was of interest to them.

Lilly noted that Novo Nordisk clearly acknowledged that only three out of the four potential licensed combinations of liraglutide were in fact discussed. Indeed, Novo Nordisk appeared to have elected to selectively omit information indicating the weight gain associated with liraglutide 1.2mg plus glimepiride on the premise that this was a 'weight neutral combination' and that the statistically significant difference vs placebo 'could hardly be considered to be clinically relevant'. The cherry-picking of the data, for what was the main maintenance dosage of liraglutide, misled readers by omission and was inaccurate.

Lilly stated that it was important to appreciate that the material was also aimed at consumer journalists and audiences. Whilst Lilly acknowledged the benefits of weight loss associated with the GLP-1 analogues and the validity of discussing this additional benefit in the management of type 2 diabetes in a balanced and fair manner, the materials at issue implied that liraglutide was indicated as a weight loss treatment over and above that for glycaemic control, which was not so. The latter, alongside some of the exaggerated discussion of the magnitude of the weight loss associated with liraglutide, could reasonably lead a consumer audience to believe that liraglutide could normalise body weight or reduce it to an extent that altered their cardiovascular risk in a significant and/or meaningful manner.

APPEAL BOARD RULING

The Appeal Board noted that both Novo Nordisk's written submission and its representatives at the appeal referred to pre-vetting of some materials by the MHRA. The Chairman noted that pre-vetting by the MHRA did not preclude consideration of a complaint under the Code nor did it preclude rulings of breaches of the Code. This was conceded by the company representatives.

The Appeal Board noted from the Novo Nordisk representatives at the appeal that all of the media backgrounders were provided as a package with a copy of the Victoza SPC in a single folder. This had not been clear in Novo Nordisk's previous submissions. A copy of the folder had not been provided to the Panel or the Appeal Board.

The Appeal Board noted that the paragraph at issue in both the 'Victoza' and 'Incretins' backgrounders stated that 'Victoza lowers glucose levels by stimulating the release of insulin only when glucose levels become too high. Victoza's impact on HbA1c control, weight loss, reduction in systolic blood pressure (SBP) and improved beta cell function has been consistently demonstrated throughout the phase 3a LEAD (Liraglutide Effect and Action in Diabetes) trials'.

The Appeal Board considered that the first sentence set out the licensed indication for Victoza. The following sentence then referred to some of the additional benefits of Victoza, as discussed in the

SPC. The Appeal Board did not consider that the statement at issue implied that Victoza could be prescribed as much for its additional benefits as for its licensed indications. The Appeal Board considered that the statement was not inconsistent with the Victoza SPC and ruled no breach of Clause 3.2 of the Code. The appeal on this point was successful.
The Appeal Board noted that the 'Incretins' backgrounder did not quantify weight loss. Given the association between excess body weight and type 2 diabetes it was important that potential weight loss was quantified. In that regard the 'Incretins' backgrounder was not capable of substantiation and the Appeal Board upheld the Panel's ruling of a breach of Clause 7.4. The appeal on this point was unsuccessful.

The Appeal Board noted that unlike the 'Incretins' backgrounder the 'Victoza' backgrounder provided some quantative data on weight changes from Marre *et al* (LEAD 1), Nauck *et al* (LEAD 2) and Zinman *et al* (LEAD 4). Buse *et al* (LEAD 6) was also mentioned but detailed data was not included. Weight change ranged from -2.8kg (1.8mg liraglutide plus metformin, LEAD 2) to +0.3kg (1.2mg liraglutide, LEAD 1). Weight loss was reported in three of the four studies included. The Victoza SPC stated that weight loss ranged between 1 and 2.8kg. The Appeal Board did not consider that the 'Victoza' backgrounder implied that every patient on Victoza would lose weight. The Appeal Board noted that whilst the 'Victoza' backgrounder did not reflect the totality of the weight change data sufficient information was given such that the backgrounder was not misleading, exaggerated or incapable of substantiation on this point. The Appeal Board ruled no breach of Clauses 7.2, 7.3, 7.4 and 7.10. The appeal on this point was successful.

The Appeal Board noted that both the medical and the lay press releases stated under a section headed 'Additional benefits' that 'Victoza can help patients achieve weight loss by increased satiety and delayed gastric emptying, and thus reduce caloric intake'. This was described as an important factor in treating type 2 diabetics as many were overweight. The Appeal Board noted that the press releases each included a section on 'Comparative Studies' which detailed the results of Buse *et al* (LEAD 6) in which a direct comparison between Victoza and exenatide found that both treatments led to a 3kg weight loss during the 26-week study. No further details of weight loss/gain were quantified. The Appeal Board noted that the Victoza SPC stated that weight loss ranged between 1.0 and 2.8kg. The Appeal Board noted that Novo Nordisk had accepted the Panel's ruling of a breach of Clause 7.2 regarding the data on weight loss in the press releases. Notwithstanding this ruling the Appeal Board did not consider that overall the data on weight in the press releases was incapable of substantiation or constituted a misleading comparison; the Appeal Board ruled no breach of Clauses 7.3 and 7.4. The appeal on this point was successful.

The Appeal Board noted that the health professional's statement in the press releases that '…patients with type 2 diabetes can be confident they are controlling their blood sugar, and may benefit from weight loss. This is an important advance for patients type 2 diabetes, many of whom are overweight' appeared in the 'additional benefits' section of both press releases. The Appeal Board noted that Novo Nordisk had accepted the Panel's ruling of a breach of Clauses 7.2, 7.3 and 7.10 on this point. The Appeal Board noted that Victoza was indicated for the treatment of type 2 diabetes and that its SPC referred to weight loss. The Appeal Board did not consider that the claim was incapable of substantiation and no breach of Clause 7.4 was ruled. The appeal on this point was successful.

The Appeal Board did not consider that the press releases were either inconsistent with the SPC or misleading about the licensed indication. The Appeal Board ruled no breaches of Clauses 3.2 and 7.2. The appeal on this point was successful.

The Appeal Board did not consider that the tone of the press releases was inappropriate. The Appeal Board noted its rulings regarding weight change. The Appeal Board did not consider that the claims in effect had turned the press release into an advertisement for a prescription only medicine. The Appeal Board ruled no breach of Clause 22.1. The appeal on this point was successful.

2 Article on Telegraph.co.uk 'New drug for type 2 diabetes helps with weight loss'

COMPLAINT

Lilly referred to its comments in point A1 above. The title 'New drug for type 2 diabetes helps with weight loss', the subheading 'A new once a day drug for type 2 diabetes which also helps patients lose weight and control blood pressure, has been launched in Britain' and the content and quotations from the Novo Nordisk spokespersons invited the reader to understand that liraglutide was licensed in the UK both as an anti-obesity treatment and an antihypertensive in patients with type 2 diabetes.

The overarching emphasis on obesity and the weight reduction benefit associated with liraglutide was unbalanced and misleading. Again, the implicit message was that obesity, per se, was the primary and only cause of type 2 diabetes and that the primary goal of liraglutide treatment was to impact this, as opposed to achieving glycaemic control in combination with other antidiabetic agents.

Unqualified and sweeping generalisations such as '… the traditional drugs used to control [type 2 diabetes] often encourage more weight gain' misled the reader and disparaged products such as Byetta, which was associated with an additional weight loss benefit in the management of glycaemic control in type 2 diabetes, and metformin which, at worst, had

a neutral impact on weight. This statement was also an implied criticism of insulin therapy which, as per Lilly's previous comments, might be an unavoidable therapeutic option for many patients with type 2 diabetes.

This type of message was irresponsible and might alarm a lay audience. Indeed this particular quotation suggested that current National Institute for Health and Clinical Excellence (NICE) guidelines, which recommended the use of metformin, sulphonylureas and insulin, should be ignored in preference to using liraglutide. Again, statements such as '[liraglutide] is an important advance' exaggerated the facts and misled by suggesting that liraglutide represented an important novel therapeutic advance with respect not only to weight reduction benefits but also glycaemic control. The precise importance or advance conferred by the availability of liraglutide was difficult to gauge given that it was the second GLP-1 analogue to be marketed and that both the injectable dosage form and the once-daily dosage were neither unique nor novel with respect to other currently available injectable and oral antidiabetic products.

Lilly alleged that the article effectively promoted liraglutide and advertised its weight reduction and blood pressure lowering benefits whilst largely ignoring the most important message for this readership which was that the major problem affecting type 2 diabetics was the need to achieve adequate glycaemic control in order to delay the onset of long-term complications such as heart disease; this would be consistent with the SPC.

The likely promotional nature of the media and speaker briefing materials was also evidenced by three separate mentions of the brand name and the statement that 'It costs £78.48 per month'. This information was not relevant to a consumer audience and suggested that Novo Nordisk's media briefing materials, which should not be promotional, included prescribing information which was contrary to the Code. Notwithstanding the latter, it was also incomplete and indirectly invited the reader to consider the relative cost of liraglutide compared with other antidiabetic treatments. It was implied that liraglutide could be used as monotherapy.

Again, this particular article and the Novo Nordisk spokespersons did not present a relevant and balanced discussion of the risks and benefits associated with liraglutide. The statement that '… [liraglutide] reduces the likelihood of hypoglycaemic attacks' was misleading by omission and minimised the very common or common occurrence of hypoglycaemia when liraglutide was combined with glimepiride, metformin and glimepiride, or metformin and rosiglitazone as indicated in the SPC.

Lilly alleged that this article and the quotations attributed to opinion leaders (one of whom was from a named patient organisation) were based on misleading, unbalanced and inaccurate media and speaker briefing materials developed by Novo Nordisk and therefore constituted a breach of Clauses 3.2, 7.2, 7.3, 7.4, 7.9, 7.10, 8.1, 12.1, 22.1, 22.3 and 22.5.

RESPONSE

Novo Nordisk referred to its response at point A1 above as to the materials provided by Novo Nordisk, and the fact that Novo Nordisk did not have any editorial control with regard to the final article.

Nevertheless, Novo Nordisk submitted that the title of the article 'New drug for type 2 diabetes helps with weight loss' was not ambiguous and did not imply that liraglutide was a licensed anti-obesity treatment. It was a new medicine, and in line with the SPC it could help with weight loss.

Novo Nordisk believed that health professionals would agree with the statement that 'traditional drugs used to control [type 2 diabetes] often encourage more weight gain'. The statement referred to classic agents such as sulphonylureas, thiazolidinediones and insulin which health professionals widely acknowledged to be associated with weight gain.

Novo Nordisk disagreed with Lilly that the article invited the reader to ignore the current NICE recommendations. Lilly had not asserted how the article invited the readers to ignore the current NICE guidelines, and which parts of the NICE guidelines the reader was invited to ignore. Further, Novo Nordisk considered that liraglutide represented a novel therapeutic advancement in the treatment of type 2 diabetes, as the other currently available GLP-1 analogue, exenatide could not be used once-daily in contrast to liraglutide.

Novo Nordisk did not agree that the article invited the reader to understand that liraglutide was licensed as an anti-obesity and antihypertensive agent for patients with type 2 diabetes, for the reasons set out above. It therefore denied that this article was in breach of the Code as alleged.

PANEL RULING

The Panel noted its comments and rulings in point A1 above regarding the press pack which it considered also applied here. These rulings were appealed.

The Panel had not been informed whether or not the named patient organisation had attended the launch or what materials Novo Nordisk had provided to that organisation. The Panel's rulings in Point A1 above related to Novo Nordisk's press pack.

The opinion leader from the patient organisation, quoted in the article at issue, was not a Novo Nordisk spokesperson. The Panel decided that on the information before it Novo Nordisk was not

responsible under the Code for these comments. No breach of the clauses of the Code cited by Lilly (Clauses 3.2, 7.2, 7.3, 7.4, 7.9, 7.10, 8.1, 12.1, 22.1, 22.3 and 22.5) was ruled in that regard.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that this article was, in part, a consequence of the Media Backgrounder Package addressed in A1 above and its position taken in A1 was repeated in relation to this article.

COMMENTS FROM LILLY

There were no comments from Lilly.

APPEAL BOARD RULING

The Appeal Board noted its comments and rulings in Point A1 above regarding the press pack which it considered also applied here.

3 Television interview, ITV, This Morning, 15 July 2009

COMPLAINT

Lilly alleged that the comments in this interview were based upon inaccurate and misleading media and speaker briefing materials provided by Novo Nordisk.

The individual concerned was alleged to be a Novo Nordisk spokesperson as evidenced by quotations attributed to him which he made on behalf of Novo Nordisk at the launch meeting. In the interview of 15 July 2009 his comments effectively promoted liraglutide to consumers. Statements such as '… the experts are saying it's going to transform the management of diabetes' exaggerated the facts and raised unfounded hopes and expectations of successful treatment with liraglutide. Further, comments from the programme's co-presenter such as 'Victoza it's called, if that's appropriate for you, and you must go and talk to the doctor about it' encouraged members of the public to ask doctors to prescribe liraglutide. This discussion of liraglutide was unbalanced and invited an unfair and misleading comparison by highlighting the positive benefits associated with liraglutide compared with insulin therapy. Insulin therapy was discussed as a 'problem', unlike liraglutide, and to emphasise this point viewers were told about hypoglycaemia, meal-time dosing restrictions and weight gain associated with insulin. A lay audience could reasonably surmise that liraglutide was better than insulin therapy and obviated the need for insulin therapy in all patients with type 2 diabetes. Indeed, the latter was further emphasised by the significant focus on the weight and blood pressure reduction benefits associated with liraglutide which when discussed, elicited an exclamation of 'Wow!' from the co-presenter who was a well known proponent of the weight loss and dieting lobby.

Lilly alleged that this interview was based on misleading, unbalanced and inaccurate media and speaker briefing materials developed by Novo Nordisk and therefore constituted a breach of Clauses 3.2, 7.2, 7.3, 7.4, 7.9, 7.10, 8.1, 12.1, 22.1, 22.2, 22.3 and 22.5.

RESPONSE

Novo Nordisk referred to the comments in Point A1 with regard to the content of the interviews by the independent health professionals and the quotations detailed within the above publications made by external health professionals.

Novo Nordisk had no input into the content of the interviews or the articles referred to above, other than provision of the briefing packs.

Novo Nordisk was committed to ensure the extensive media backgrounder press packs and the press releases, for the medical media and for lay press provided accurate information about type 2 diabetes, the company and the licensed indication for liraglutide, to ensure that the information provided to journalists was accurate, balanced and fair and not 'inaccurate and misleading' as alleged by Lilly. An external agency assisted Novo Nordisk and the content was pre-vetted by the Medicine and Healthcare products Regulatory Agency (MHRA). Amendments were requested by the MHRA, and these were made before the materials were released.

Novo Nordisk submitted that these activities were not in breach as alleged.

PANEL RULING

The Panel noted its comments and rulings in point A1 above regarding the press pack which it considered also applied here. These rulings were appealed.

The interview in question was with a media doctor who had spoken at the launch meeting and had provided interviews. It did not appear that his appearance on the programme was specifically due to his role with Novo Nordisk at the launch of Victoza. It appeared to be due to his regular role as the programme's commentator on medical matters. The position was unclear. The Panel considered that given Novo Nordisk had selected the individual as a speaker in relation to the launch of Victoza it was difficult to argue that, on this occasion, when speaking about Victoza, he was entirely independent from the company. The Panel considered that the item in question placed undue emphasis on the weight reduction effects of Victoza and this was extremely concerning. Novo Nordisk had provided much information about the product to the individual who was a spokesperson for Novo Nordisk at its press conference and follow up interviews. The Panel was extremely concerned about what was said in the interview and decided that the comments were covered by the rulings in A1 above. These rulings were appealed.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that this interview was, in part, a consequence of the Media Backgrounder Package addressed in A1 above and its position taken in A1 was repeated in relation to this interview.

COMMENTS FROM LILLY

There were no comments from Lilly.

APPEAL BOARD RULING

The Appeal Board noted its comments and rulings in Point A1 above regarding the press pack which it considered also applied here.

Given Novo Nordisk's submission the Appeal Board questioned the briefing. Nonetheless, the Appeal Board made no additional ruling on the comments of the individual, who it considered had acted as a Novo Nordisk spokesperson, as it considered that the matter was covered by its reference to Point A1 above.

4 Radio interviews, BBC Radio Ulster, Good Morning Ulster, 7 July 2009

COMPLAINT

Lilly stated that from the outset, the content of this consumer programme promoted and advertised the weight reduction benefits associated with liraglutide. The discussion opened with a health professional stating that '… common discomforts for diabetes include the weight gain much of their medication can cause ...' and was followed by 'Hopefully though not any more, a new drug called Victoza for people suffering with type 2 diabetes is being released today'. This health professional also emphasised that liraglutide '…will help patients with diabetes control their weight which is a major problem'. Again, wording such as 'This treatment really is a major step forward ...' exaggerated the facts and misled by suggesting that liraglutide represented an important novel therapeutic advance with respect not only to weight reduction benefits but also glycaemic control. The step forward offered by liraglutide was difficult to gauge given that it was the second GLP-1 analogue to be marketed and the fact that both the injectable dosage form and the once-daily dosage were neither unique nor novel with respect to other currently available injectable and oral antidiabetic products. The implication was that liraglutide offered benefits that were currently unavailable for example with products such as Byetta.

Comments from the health professional sought to engender confidence in the safety of liraglutide by exaggerating that the testing and development of liraglutide had '… been one of the most extensive programmes of development that we have seen in diabetes ...'; this claim was disparaging, was unsubstantiated and misled the lay audience by suggesting that this was a quality standard not applicable to, or achieved by, other licensed antidiabetic agents.

The comments from the health professional did not set out a relevant and balanced discussion of the risks and benefits associated with liraglutide. The statement that '… the risk therefore of developing low blood sugars or hypoglycaemia which many people with diabetes will have heard about is extremely low' was misleading by omission.

Given the intended audience the health professional did not mention the safety and tolerability of this new treatment particularly with regard to the incidence of gastrointestinal side effects, which occurred very commonly, and hypoglycaemia which occurred commonly or very commonly when liraglutide was used in combination with glimepiride, metformin and glimepiride or metformin and rosiglitazone; this would have provided balance to the interview.

The health professional discussed that 'The early studies that we've seen and the early data that we have suggest that maybe [liraglutide] might do something about the progression of the disease. We know that type 2 diabetes doesn't stand still, it's a condition that gets worse year on year, and there's increasing evidence to suggest that this new type of treatment may actually delay that progression' and '... it seems as though this new treatment, Victoza, may preserve beta cell function and may even improve beta cell function and therefore stop the condition progressing and stop the likelihood of patients needing to go onto more complex treatment such as insulin'. The assertion that liraglutide could stop the condition progressing and the discussion of the putative mechanisms which might underlie the observations from the early studies constituted the off-licence promotion of liraglutide to the public. Lilly noted that Byetta was the first-in-class of this type of treatment and not liraglutide, as was implied in this statement.

Lilly alleged that this interview and the quotations attributed to the health professional were based on misleading, unbalanced and inaccurate media and speaker briefing developed by Novo Nordisk and therefore constituted a breach of Clauses 3.2, 7.2, 7.3, 7.4, 7.9, 7.10, 8.1, 12.1, 22.1, 22.3 and 22.5.

RESPONSE

Novo Nordisk referred to its response in point A3.

PANEL RULING

The Panel noted its comments and rulings at point A1 above regarding the press pack which it considered also applied here. These rulings were appealed.

The interview in question was with a health professional who had been briefed by Novo Nordisk

to give interviews in relation to the Victoza launch. The Panel was concerned that the health professional had stated that Victoza 'will also help them control their weight which is a major problem'. The spokesperson stated that Victoza was a major step forward. The Panel queried whether this was so. It was the second GLP-1 medicine to be launched but the first to be administered once a day. The Panel considered that Novo Nordisk was responsible under the Code for the comments made by the health professional. The Panel considered that the allegations about what was said by the health professional with regard to Victoza's effect on weight and it being a major advance in therapy were covered by its rulings in point A1 above.

The Panel noted that the health professional had stated that Victoza had undergone 'one of the most extensive programmes of development that we've seen in diabetes, probably well over ten years now that's …'. In the Panel's view this statement implied that Victoza had undergone a more extensive development programme than other antidiabetic medicines. There was no information before the Panel to substantiate this implied comparison. The Panel considered that the statement was misleading and that it disparaged other medicines. Breaches of Clauses 7.2, 7.3, 7.4 and 8.1 were ruled.

The Panel considered that the health professional's statement that the risk of developing hypoglycaemia was extremely low was misleading with respect to the safety of Victoza. The SPC stated that hypoglycaemia was common and very common when Victoza was used in combination with a sulphonylurea. The Panel ruled a breach of Clauses 7.2 and 7.9 of the Code. The Panel further noted that in response to the question 'And how long has it been trialled for? There's a lot of concern sometimes about side-effects' the health professional did not refer to the side effect profile of Victoza, in particular he did not discuss the common or very common gastrointestinal effects of the medicine. The Panel considered that the answer to the question was misleading by omission and ruled a breach of Clause 7.2.

The Panel noted that the health professional had stated that Victoza might stop type 2 diabetes progressing and stop the likelihood of patients needing to go onto insulin. There was no data before the Panel to show that this was so. Although beta-cell function improved with Victoza it had not been demonstrated that, patients would not need to progress onto insulin therapy. The Panel considered that the statement was misleading and exaggerated. A breach of Clauses 7.2 and 7.10 was ruled.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that this interview was, in part, a consequence of the Media Backgrounder Package addressed in A1 above and its position taken in A1 was repeated in relation to this interview.

Novo Nordisk did not appeal any of the specific rulings with respect to these radio interviews.

COMMENTS FROM LILLY

There were no comments from Lilly.

APPEAL BOARD RULING

The Appeal Board noted its comments and rulings in Point A1 above regarding the press pack which it considered also applied here.

5 Article in The Pharmaceutical Journal 'Liraglutide launched as new option for uncontrolled diabetes'

COMPLAINT

Lilly alleged that this article was aimed at health professionals and was evidently based on the launch briefing in London. Lilly alleged that the inaccurate, misleading and unbalanced reporting of liraglutide with particular regard to discussion of the incidence of severe hypoglycaemia and weight loss were the result of inaccurate, misleading and promotional media and speaker briefing materials provided by Novo Nordisk.

The statement that liraglutide was '… the first once-daily human glucagon-like peptide-1 (GLP-1) analogue to be made available' misled the reader by omission. In the absence of any mention of Byetta the impression created by this wording was that liraglutide was the first licensed product in this particular class.

One of the health professional's quoted in this article was reported to have claimed that when liraglutide was used with metformin 'severe hypoglycaemia is virtually unheard of' and 'almost impossible' because of the medicine's glucose-dependant action. This statement was promotional in nature, selective, misled by omission and exaggerated the relevance and importance of clinical trial observations to what might be observed in real-life clinical practice. There was also no reference to the equally important observation that hypoglycaemia occurred commonly or very commonly when liraglutide was used in combination with glimepiride, metformin and glimepiride or metformin and rosiglitazone.

In the absence of this clarification and given the credibility and gravitas lent to this opinion by a respected physician, readers might reasonably assume that the risk benefit associated with liraglutide in combination with other antidiabetics was similar. Indeed this focus on severe hypoglycaemia served to obfuscate from a discussion of the incidence of gastrointestinal side-effects which occurred very commonly and were particularly important with regard to GLP-1 receptor agonists. This was a breach of Clauses 7.2, 7.3 and 7.9.

The health professional was also reported to have stated that 'The other big advantage, which patients really appreciate, is if you use this drug in combination with metformin you're getting very nice weight loss, which you are noticing already at two weeks and continues at 26 weeks compared with sulphonylurea combination where you are getting weight gain. And that difference is 3.6kg ...'. Again, in the absence of any discussion of the glycaemic control associated with liraglutide, this statement placed undue emphasis on the benefit of weight loss and suggested that this should be the primary therapeutic consideration. Further, the claim that patients would really appreciate this was pure supposition that required substantiation.

This statement was misleading, inconsistent with the SPC and did not represent the balance of evidence with respect to the specific numerical benefit in weight loss reported. This claim referred to data from a single study that had been cherry-picked from a single 26 week study to compare the efficacy and safety of liraglutide, glimepiride and placebo, all in combination with metformin in patients with type 2 diabetes; patients were randomised to receive once-daily liraglutide (0.6, 1.2, or 1.8mg/day) in combination with metformin, metformin monotherapy, or combination therapy of metformin and glimepiride. This claim misled by omission and exaggerated the results in the absence of any indication of the baseline body weight and BMI by which the implied clinical and statistical significance of the reductions referred to could be assessed (Lilly referred to point B3 below with regard to item number UK/LR/0409/0079).

The wording of this statement also suggested that the weight loss observed was sustained beyond 26 weeks; this could not be substantiated. Further, it was not clear that the reported weight loss referred to a mean observed only with the 1.2mg dosage of liraglutide and not the 0.6mg dose that this, all embracing, statement implied. This unqualified statement also misleadingly suggested that this comparison of liraglutide was with all available sulphonylureas and not specifically in combination with glimepiride.

Further, selectively promoting the result from a single study of liraglutide was misleading and exaggerated the benefits of liraglutide with regard to the weight loss benefit observed in other studies and was inconsistent with the manner in which it was discussed in the liraglutide SPC. The latter stated that 'Victoza in combination with metformin, metformin and glimepiride or metformin and rosiglitazone was associated with sustained weight reduction over the duration of studies in a range from 1.0kg to 2.8kg'; this wording more appropriately and fairly represented the balance of evidence regarding the weight loss observed with different dosages of liraglutide when combined with other antidiabetic treatments.

Lilly alleged that this was in breach of Clause 3.2, 7.2, 7.3, 7.4 and 7.10.

RESPONSE

Novo Nordisk referred to its response in point A3.

PANEL RULING

The Panel noted its comments and rulings in point A1 above regarding the press pack which it considered also applied here. These rulings were appealed. The article quoted a health professional speaking at the launch meeting. Novo Nordisk had not commented on the accuracy of the quotations despite its responsibility for what was said. The Panel was concerned that statements that 'severe hypoglycaemia was virtually unheard of' and 'almost impossible' were inconsistent with the data in the SPC which referred to hypoglycaemia when liraglutide was combined with metformin and glimepiride as very common and as common when liraglutide was combined with metformin and rosiglitazone. The SPC stated that major hypoglycaemia had primarily been observed when liraglutide was combined with a sulphonylurea.

The Panel was also concerned that the statements regarding weight loss were inconsistent with the SPC.

The Panel considered that the allegations about what was said by the health professional were covered by its rulings in points A1 and A4 above. These rulings were appealed.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that this article was, in part, a consequence of the Media Backgrounder Package addressed in A1 above and its position taken in A1 was repeated in relation to this article.

COMMENTS BY LILLY

There were no comments from Lilly.

APPEAL BOARD RULING

The Appeal Board noted that the article in The Pharmaceutical Journal included the claim '… when liraglutide is used with metformin "severe hypoglycaemia is virtually unheard of" and "almost impossible" because of the drug's glucose-dependent action'. This claim was attributed to a health professional speaking at the Victoza launch meeting. The Appeal Board was concerned that the claim was inconsistent with the SPC, which referred to hypoglycaemia as very common when liraglutide was combined with metformin and glimepiride and as common when liraglutide was combined with metformin and rosiglitazone. The SPC stated that major hypoglycaemia had primarily been observed when liraglutide was combined with a sulphonylurea. The Appeal Board considered that the claim at issue was misleading and ruled breaches of Clauses 7.2 and 7.9. The appeal on this point was unsuccessful. The Appeal Board did not consider, however, that there

was a misleading comparison and therefore ruled no breach of Clause 7.3. The appeal on this point was successful.

The Appeal Board noted that the article quoted the health professional as stating that 'The other big advantage, which patients really appreciate, is if you use this drug in combination with metformin you're getting very nice weight loss, which you are noticing already at two weeks and continues at 26 weeks, compared with sulphonylurea combination where you are getting weight gain, and that difference is 3.6 kg'. The Appeal Board noted Section 5.1 of the Victoza SPC stated that Victoza in combination with metformin, metformin and glimepiride or metformin and rosiglitazone was associated with sustained weight reduction over the duration of the studies in a range from 1.0kg to 2.8kg. The Appeal Board noted its rulings in Point A1 above. It did not consider that the claim was inconsistent with the Victoza SPC and ruled no breach of Clause 3.2. The appeal on this point was successful.

However, the Appeal Board considered that the claim was misleading as it implied that all patients would experience weight loss at two weeks and that was not so and that the comparison of liraglutide plus metformin was with liraglutide plus all available sulphonylureas and not specifically in combination with glimepiride. The Appeal Board considered that the claim was misleading and ruled breaches of Clauses 7.2 and 7.3. The appeal on this point was unsuccessful. The Appeal Board noted that the Victoza SPC referred to weight reduction and thus it considered that the claim was capable of substantiation and ruled no breach of Clause 7.4. The appeal on this point was successful. However the Appeal Board considered that the claim was exaggerated. The Appeal Board ruled a breach of Clause 7.10. The appeal on this point was unsuccessful.

6 Article in Clinical Pharmacist 'Liraglutide added to type 2 diabetes arsenal'

COMPLAINT

Lilly alleged that this article, aimed at health professionals, was clearly based on the inaccurate and misleading Novo Nordisk press briefing. The article reported comments by a pharmacist regarding the results of new study data comparing liraglutide with exenatide published in the Lancet (Buse *et al* 2009) LEAD 6.

This open-label study involved adults with inadequately controlled type 2 diabetes on maximally tolerated doses of metformin, sulphonylurea, or both, who were stratified by previous oral antidiabetic therapy and randomly assigned to receive additional liraglutide 1·8mg once a day or Byetta 10mcg twice a day in a 26-week open-label, parallel-group, multinational study.

The primary outcome was change in HbA1c. The quotations attributed to the pharmacist failed to qualify that the outcome associated with liraglutide was specific only to the 1.8mg dosage; this was misleading by omission and exaggerated the benefits to imply that the results and comparison with Byetta were also applicable to the 0.6 or 1.2mg dosages of liraglutide. Further there was a failure to qualify and consider the limitations of the open-label study design with respect to the efficacy and safety outcomes reported.

This was in breach of Clauses 3.2, 7.2, 7.3, 7.4, 7.9, 7.10, 8.1, 12.1, 22.1, 22.3 and 22.5.

RESPONSE

Novo Nordisk did not refer to this article in its response.

PANEL RULING

The Panel noted that the pharmacist quoted in the article was not one of the spokespeople who Novo Nordisk had submitted that it had used at the launch of Victoza. The Panel did not know whether the health professional had been provided with a press pack. The Panel decided on the information before it that Novo Nordisk was not responsible under the Code for the comments attributed to the health professional. There was no evidence that Novo Nordisk had provided any material to the health professional. No breach of the clauses of the Code cited by Lilly was ruled.

The Panel noted that the article also referred to another health professional's comment at the launch briefing ie that when liraglutide was used with metformin 'severe hypoglycaemia is virtually unheard of'. The Panel considered that its ruling at point A4 of breaches of Clauses 7.2 and 7.9 with regard to the risk of developing hypoglycaemia applied here.

The Panel noted its comments in point A1 about the press materials and thus did not consider Lilly's allegations about the content of the article.

7 Article in the British Journal of Cardiology 'Liraglutide: novel drug for type 2 diabetes launched' and general allegations

COMPLAINT

Lilly alleged that this article, aimed at health professionals, was clearly based on the inaccurate and misleading Novo Nordisk press briefing. The article referred to the fact that Novo Nordisk described liraglutide as 'a revolutionary product' and that it worked in a unique way. Both these claims were exaggerated and could not be substantiated. The revolution or uniqueness offered by liraglutide was difficult to gauge given that it was a second-in-class GLP-1 receptor agonist and the fact that both the injectable dosage form and the

once-daily dosage were neither unique nor revolutionary with respect to other currently available injectable and oral antidiabetic products. It was implied that liraglutide offered benefits that were currently unavailable for example with products such as Byetta. The statement that liraglutide was the first once-daily human GLP-1 analogue for the treatment of type 2 diabetes was alleged to be misleading by omission. With no reference to Byetta it was implied that liraglutide was first licensed product in this particular class.

It appeared that the Novo Nordisk press and speaker briefing materials facilitated the promotion of generalised and unqualified statements, regarding the substantial lowering of fasting and postprandial glucose concentrations, overall reduction in HbA1c of up to 1-2%, the associated reduction in weight and systolic blood pressure of about 7mmHg observed during the extensive clinical development programme for liraglutide. The LEAD study programme comprised six different studies. These studies employed different designs, different dosages of liraglutide, various comparators and dosages of these and differing efficacy/safety outcomes amongst many other variables. These qualifications were important and their absence in the context of promotional claims misled by omission and exaggerated the facts. For example the quoted 2% reduction in HbA1c did not represent the balance of evidence from the LEAD studies. Similarly, the figure for the reduction in blood pressure did not reflect the lower end of the range of 2.3mmHg and thus overstated the clinical significance of this observation. Further, the absence of baseline study subject demographics misled with regard to the implied clinical and statistical significance of the outcomes discussed.

Lilly questioned the accuracy, appropriateness, objectivity and balance of the Novo Nordisk speaker briefing in light of some of the quotations. This was exemplified by a quotation attributed to a health professional that liraglutide works so well 'and ticks so many boxes that it was almost too good to be true'. This was an unqualified promotional claim that exaggerated the facts and could not be substantiated. Again, as discussed in point A5 above, such quotations misrepresented and minimised the risk of hypoglycaemia associated with liraglutide.

The same health professional also made the promotional claim that the posology and method of administration '… should improve patient compliance and, in turn, clinical outcomes'. This assertion could not be substantiated with respect to liraglutide and was conjecture and hypothesis. The health professional also stated that it would be 'incredibly disappointing' if primary care trusts (PCTs) were to restrict the use of liraglutide and not have it widely prescribed prior to the result of NICE Technology Appraisal which was due in 2010; clearly this was a position endorsed by Novo Nordisk. Lilly alleged that this was wholly irresponsible and entirely inconsistent with the requirement of pharmaceutical companies to establish good working relationships with partners within the NHS and the Department of Health (DoH) to support and encourage the rational and safe use of new 'black triangle' treatments.

Finally, a quotation attributed to another health professional with the article, stated that the introduction of liraglutide might well 'change the lives of many diabetic patients' for the better. This was an unqualified, exaggerated promotional claim that could not be substantiated. Further, it disparaged existing antidiabetic agents and suggested that they did not deliver a positive change or improvement to diabetic patients.

Given the serious nature of the matter Lilly alleged that the media activity undertaken by Novo Nordisk, through its agents and spokespersons represented a breach of Clauses 2 and 9.1.

Lilly also believed that the media activity constituted a breach of the MHRA Blue Guide on the Advertising and Promotion of Medicines in the UK, which prohibited the promotion of prescription only medicines to patients and the public.

Lilly noted that in its response, Novo Nordisk indicated that it had decided to share the 'relevant' parts of Lilly's complaint of 4 September 2009 with the health professionals mentioned in what was a confidential inter-company communication. This was entirely inconsistent with the tenet and spirit of Paragraph 5.2 of the Constitution and Procedure. Indeed, Lilly questioned why, in the spirit of openness and transparent discussions Novo Nordisk had only shared selected aspects of its extensive complaint detailing the misleading promotion of liraglutide with those health professionals. Lilly regarded this as a serious attempt by Novo Nordisk to tarnish Lilly's reputation. Lilly categorically refuted the allegation that its intention was to disparage any of the health professionals mentioned in its complaint. The latter simply highlighted examples of how these health professionals might have been informed by misleading and inaccurate media and speaker briefing materials developed by Novo Nordisk and/or its agent(s); or indeed were not briefed at all. Lilly considered that the serious and premeditated breach of the Constitution and Procedure by Novo Nordisk represented a breach of Clauses 2 and 9.1.

RESPONSE

Novo Nordisk referred to its response at point A3.

Novo Nordisk disagreed with Lilly's view that Novo Nordisk had gone against the spirit and tenet of Paragraph 5.2 of the Constitution and Procedure, which Lilly considered implied that inter-company communications must remain confidential between the parties [see last paragraph of complaint at Point A7 below]. Paragraph 5.2 did not state that

inter-company communications must remain confidential between the parties, nor was Lilly's correspondence marked 'Confidential'. Novo Nordisk considered it both reasonable and important for it to approach the health professionals about whom the allegations were made, in order to fully investigate the allegations, to ensure its response was both informed and accurate. Further, Lilly alleged that the independent health professionals were also liable for the misleading and inaccurate information provided during the interviews. As such, Novo Nordisk believed it had a duty to inform these health professionals as to the allegations made by Lilly.

PANEL RULING

The Panel noted that Lilly had made a number of allegations regarding the content of the article at issue but had not cited those clauses of the Code which it considered had been breached other than a general reference to its allegations in A5 that the risk of hypoglycaemia associated with liraglutide was misrepresented and minimised. In the absence of clearly cited clauses the Panel decided that it could not make any rulings. Nonetheless the Panel noted its comments above about the press pack and asked that Novo Nordisk be advised that it had similar concerns here.

With regard to Lilly's comments about the MHRA Blue Guide the Panel noted that it could only consider the allegations in relation to the Code and not the MHRA Blue Guide or UK law. Finally, the Panel did not consider that it was inconsistent with Paragraph 5.1 of the Constitution and Procedure for Novo Nordisk to provide the health professionals used at the launch with details of the complaint. The Panel had not been given details of what Novo Nordisk had provided to the health professionals. As a principle it was not necessarily unacceptable under the Code. The Panel considered that, in relation to this allegation, Lilly had not proven its complaint on the balance of probabilities. No breach of Clauses 2 and 9.1 was ruled.

Lilly had referred to the media activity in total and alleged breaches of Clauses 9.1 and 2.

With regard to these general allegations, the backgrounders referred to above and the press releases the Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled. With regard to Clause 2, which was used as a sign of particular censure, the Panel considered that issuing misleading material to the press was a serious matter as was issuing a press release that advertised a prescription only medicine to the public. The Panel thus ruled a breach of Clause 2 which was appealed.

APPEAL BY NOVO NORDISK

Novo Nordisk noted that no breaches were ruled in respect of the specific article but the Panel ruled a breach of Clause 2 of the Code in relation to the Media Backgrounder Package generally.

Novo Nordisk noted that Clause 2 indicated the Panel's view of the gravity of the alleged breaches. However Novo Nordisk contended that as it had successfully dealt with several of the Panel's concerns on a point by point basis and the great majority of the specific allegations in relation to the Media Backgrounder Package were already approved under the MHRA pre-vetting procedure, it failed to see how the Panel could form this view. Accordingly, Novo Nordisk disagreed with the Panel that the Media Backgrounder Package or any component of it was in breach of Clause 2 of the Code.

Novo Nordisk submitted that its concern regarding the discrepancy between the Panel's ruling and the MHRA pre-vetting approvals was particularly relevant in the case of the Clause 2 ruling.

COMMENTS BY LILLY

There were no comments from Lilly.

APPEAL BOARD RULING

The Appeal Board noted its rulings above and that the company had accepted a number of rulings of breaches of the Code.

The Appeal Board was concerned that it did not have all the relevant material such as the press pack folder and the presentations given at the launch meeting. Although the Appeal Board had concerns about the material Novo Nordisk had provided it did not consider overall that these warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure. No breach of Clause 2 was ruled. The appeal on this point was successful.

B Promotional Materials

1 Journal advertisement (UK/LR/0409/0087)

The advertisement at issue was a double page spread. The illustration on the left hand page was of what readers would assume to be a male doctor's hand holding the roots and trunk of a small tree whose leaves and branches had been replaced by a multi-coloured lollipop. The right hand page was headed 'Do more than lower blood glucose' followed by a box containing the following:

'Once-daily Victoza, in combination with metformin and/or a sulphonylurea, impacts on multiple factors associated with type 2 diabetes providing from baseline

- Reductions in HbA1c

And in addition

- Reductions in weight
- Reductions in systolic blood pressure
- Improvements in beta-cell function.'

Immediately below the box, in small type, were the details of the licensed indications for Victoza.

COMPLAINT

Lilly alleged that the heading 'Do more than lower blood glucose' was misleading and inconsistent with the Victoza SPC; it invited the reader to consider that Victoza was licensed to achieve something clinically more significant than glycaemic control in combination with specific antidiabetic agents in type 2 diabetic adults. The prominence of the heading misled readers about the product's licensed indication and did not encourage rational use. The text box beneath the heading invited the reader to consider that '… Victoza, in combination with metformin and/or a sulphonylurea, impacts on multiple factors associated with type 2 diabetes providing from baseline ...' and further misled and reinforced the suggestion that Victoza was additionally indicated for '… reductions in weight, reductions in systolic blood pressure'. Given this, the heading clearly invited the reader to consider Victoza as a treatment for obesity and hypertension. The precise details of the Victoza indication only became apparent by reference to a footnote which followed various promotional claims and was not directly associated with the heading. Lilly noted the relatively small font of this footnote.

The wording, design and layout of this advertisement also invited a comparison with other antidiabetic agents, which like Victoza were all principally licensed to achieve glycaemic control, and suggested that Victoza offered something more than lowering blood glucose compared with these. The significant emphasis and discussion of the weight reduction benefits associated with Victoza only served to reinforce this suggestion.

The claims about reductions in weight and systolic blood pressure also misled by omission in the absence of any indication of the baseline by which the implied clinical and statistical significance of the reductions referred to could be measured. Further, whilst the claims about the reductions in weight and systolic blood pressure observed with Victoza were contextualised by reference to combination with 'a sulphonylurea', the important qualification that this specifically related to a combination with glimepiride, and not all sulphonylureas as was implied, was missing. Without the latter these claims misled readers by omission. This tendency to generalise, without appropriate qualification, efficacy claims in support of 'once-daily Victoza' misleadingly suggested that the reductions in weight, systolic blood pressure and HbA1c were clinically and statistically significant, applicable to all patients and had been observed with all three doses of Victoza when combined, as per indication, with metformin, glimepiride or rosiglitazone; this was not so.

The visual was also misleading and inconsistent with the SPC and the licensed indication. Whilst the depiction of type 2 diabetes by analogy to a 'lollipop tree' was not unreasonable, the depiction of the tree being entirely uprooted implied that Victoza could uproot type 2 diabetes and eliminate the illness completely; Victoza was not a cure for diabetes mellitus as was inferred by the visual. Notwithstanding the latter, the visual also implied that liraglutide delayed the progression of type 2 diabetes for which it was not licensed.

For the reasons outlined above Lilly alleged that this advertisement was in breach of Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.8, 7.10, 8.1 and 9.1.

RESPONSE

Novo Nordisk stated that the majority of its promotional materials were pre-vetted and approved by the MHRA.

Novo Nordisk referred to a letter of 3 June 2009 from the MHRA which stated 'The indication should be included prominently in the main part of the stands and adverts to ensure that the audience is not misled as to the authorised indication'.

Novo Nordisk did not agree that the heading 'Do more than lower blood glucose' was misleading and inconsistent with the SPC and that the prominence of this headline misled readers about the product's licensed indication and in this regard did not encourage the rational use of liraglutide. The heading was a 'call to action', urging physicians managing type 2 diabetes to look beyond blood glucose and consider some of the widely accepted additional underlying pathologies. Further, this was approved by the MHRA, subject to inclusion of the indication in a prominent position. The indication for Victoza for the treatment of type 2 diabetes, which was taken verbatim from the SPC, was clear on the advertisement as per the MHRA's requirements.

The MHRA was happy with the box. It had commented about the draft lay out and suggested that references to other actions such as blood pressure effects were clearly separated from and subsidiary to the main indication so as not to suggest a wider indication than the SPC which Novo Nordisk did and which the MHRA approved.

Novo Nordisk disagreed that the wording, design and layout invited readers to make additional comparisons. It simply stated the clinically significant benefits beyond HbA1c control which was consistent with the SPC.

Novo Nordisk did not agree that the reference to reductions in weight and systolic blood pressure without the inclusion of the baseline parameters misled by omission. These claims simply highlighted the clinically important additional benefits of Victoza and could be substantiated by the cited randomized controlled trials (Marre *et al* 2009, Nauck *et al* 2009, Russell-Jones *et al* 2009) and Section 5.1 of the SPC.

The approval by EMEA was for all sulphonylureas even though the study was conducted with glimepiride, one of the most commonly prescribed sulphonylureas in Europe.

Novo Nordisk did not agree that the mention of the clinically and statistically relevant benefits of weight and systolic blood pressure went beyond what was supported by the SPC. There was clear reference to the clinical data that supported the clinically and statistically relevant changes for weight and systolic blood pressure. Throughout the LEAD studies the benefits of HbA1c, weight and systolic blood pressure had been seen for both Victoza 1.2mg and 1.8mg. The third dose of 0.6mg which formed a separate arm in some of the LEAD trials was only a starting (titration) dose and its benefits were not recorded as part of the SPC. No mention of dosing was contained within the advertisement so the assumption that the reader would make such a conclusion was unsubstantiated.

Novo Nordisk did not agree that the visual was inconsistent with the SPC and implied that Victoza could cure type 2 diabetes. The advertisement did not expressly or by implication convey that Victoza represented a cure for diabetes, or that it could delay disease progression.

The visual symbolized the apparent surface problem caused by type 2 diabetes - high blood glucose. It encouraged physicians to do more than treat the most obvious symptom (hyperglycaemia) but take a more holistic approach to treatment, including the additional benefits, which were contained within the SPC, that considering weight gain, blood pressure, and beta-cell function when treating patients with type 2 diabetes, inline with the recommendations of a number of diabetes associations, including EASD, IDF and American Diabetes Association (ADA). There was no mention in the advertisement that Victoza would normalize these parameters in all patients. That said, these additional product benefits were important treatment considerations that were supported by the SPC.

Further, the advertisement with the visual was approved by the MHRA.

Novo Nordisk did not agree that this advertisement breached the clauses of the Code cited by Lilly.

PANEL RULING

The Panel considered that the heading 'Do more than lower blood glucose' would encourage Victoza to be prescribed because of its effects beyond that of glycaemic control. In that regard the benefits of therapy had not been separated from or placed subsidiary to the main indication. A wider indication was implied. The reason to use Victoza, ie to reduce HbA1c, was the third piece of information on the page after the heading and the subheading which stated that 'Once-daily Victoza … impacts on multiple factors associated with type 2 diabetes …'. In the boxed text equal emphasis was given to 'Reductions in HbA1c' as to reductions in weight, systolic blood pressure and improvements in beta-cell function.

There was a difference between promoting a product for a licensed indication and promoting the benefits of using that product albeit that some of the benefits were specifically mentioned in the SPC. The Panel further noted that although the licensed indication for Victoza was for the treatment of type 2 diabetes in combination with metformin and/or a sulphonylurea or with metformin and a thiazolidinedione. The data regarding the benefits of therapy, however, was from studies using only glimepiride as the sulphonylurea and rosiglitazone as the thiazolidinedione. The Panel considered that the secondary effects on weight, systolic blood pressure and beta-cell function had not been placed sufficiently within the context of the primary reason for prescribing Victoza ie glycaemic control or within the limit of the data. This was inconsistent with the SPC and a breach of Clause 3.2 was ruled. This ruling was appealed.

The Panel did not consider that the advertisement invited a comparison with other antidiabetic medicines. The advertisement mentioned other oral antidiabetic medicines but there were no comparisons. It suggested that Victoza offered more than lowering of blood glucose but this was not necessarily unacceptable or disparaging. No breach of Clauses 7.3 and 8.1 was ruled.

The Panel noted its comments previously about weight changes in point A above (particularly in point A1). The weight changes were mean values and had not been quantified or qualified in the advertisement now at issue. The claim 'Reductions in weight' implied that this would be observed with both doses of Victoza (1.2mg and 1.8mg) in every licensed combination, was clinically and statistically significant and applicable to all patients. The claim was referenced to Nauck *et al* 2009 (LEAD 2), Russell-Jones *et al* 2008 (LEAD 5) and the SPC.

Nauck *et al* (LEAD 2) stated that weight loss was dose dependent in the liraglutide treatment groups; 2.6 ± 0.2kg and 2.8 ± 0.2kg for 1.2 and 1.8mg liraglutide combination groups respectively which was significantly different ($p<0.0001$) from the weight gain in the glimepiride group (1.0 ± 0.2kg). The weight loss in the 1.2mg and 1.8mg liraglutide combination groups was also statistically significantly greater ($p\leq0.01$) than the weight loss in the placebo group (1.5 ± 0.3kg). There was no mention of the percentage of patients which lost weight.

Russell-Jones (LEAD 5) stated that the mean weight loss, 1.8kg (SEM 0.33) in the 1.8mg liraglutide combination group (metformin plus glimepiride) was statistically significantly superior to the reduction in the placebo group (metformin plus glimepiride) 0.42kg (SEM 0.39) ($p=0.0001$). Weight increased by 1.6kg in the insulin glargine group.

The Panel did not accept that such weight loss data was needed for 0.6mg liraglutide to support the claim 'Reductions in weight'; the 0.6mg liraglutide dose was clearly a starting dose.

The Panel considered that the claim 'Reductions in weight' was too simplistic given the data. Although weight loss would benefit type 2 diabetics, the amount lost was small. Nonetheless some weight loss, however modest, was preferable compared with the weight gain associated with some other antidiabetic treatments. The SPC recorded weight gain data for Victoza 1.2mg plus glimepiride. It was important for health professionals to fully understand the magnitude of weight loss with Victoza and also that not every patient would lose weight. This was not possible from the claim at issue. The Panel considered that the claim was misleading, ambiguous and exaggerated; it could not be substantiated for each Victoza dose (1.2mg or 1.8mg) or licensed combination. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled. These rulings were appealed.

The claim 'Reductions in systolic blood pressure' was referenced to Marre *et al* (LEAD 1) 2009, Nauck *et al* (LEAD 2) and the SPC. The Panel noted its comments previously about reductions in systolic blood pressure (Point A). Marre *et al* (LEAD 1) stated that although decrease in blood pressure occurred with Victoza 1.2mg and 1.8mg combined with glimepiride (2.6 - 2.8mmHg) these were not significantly different from placebo or rosiglitazone. Nauck *et al* (LEAD 2) reported significant reductions in systolic blood pressure 2 - 3mmHg for 1.2mg and 1.8mg Victoza plus metformin compared with the increase observed with the glimepiride plus metformin group. The Victoza SPC stated that compared to active comparator the decrease in systolic blood pressure was 1.9 to 4.5mmHg.

The blood pressure changes had not been quantified in the advertisement. The claim 'Reductions in systolic blood pressure' implied that this applied to every licensed combination, was clinically and statistically significant. The SPC only referred to reductions in systolic blood pressure vs active comparator some of the results had not been statistically significantly different to placebo. It was important that health professionals fully understood the effects on blood pressure. This was not possible from the claim at issue. The Panel ruled that the unqualified and unquantified claim was misleading, ambiguous and exaggerated and could not be substantiated. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled. These rulings were appealed.

The Panel did not consider that the lollipop tree visual implied that Victoza could uproot type 2 diabetes and eliminate the illness. In the Panel's view it illustrated that there were a number of factors linked to type 2 diabetes. The Panel did not consider the visual was, in itself, inconsistent with the SPC as alleged. No breach of Clauses 3.2, 7.2, 7.4 and 7.8 was ruled.

The Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled. This ruling was appealed. The Panel did not consider the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

APPEAL BY NOVO NORDISK

Novo Nordisk noted that the Panel considered that the advertisement implied a wider use for Victoza than the actual licensed indications, by alleging that the additional benefits had not been separated from or placed subsidiary to the licensed indication.

Novo Nordisk submitted that the advertisement did separate the main indication from the wider benefits. The effect of the licensed indication (HbA1c improvement) was clearly separated from the other benefits, which were listed under the subtitle of 'Additional benefits' and not in bold font. Furthermore, the licensed indication was also clearly set out directly under the highlighted box. It was inappropriate and unjust for the Panel to rule a breach of Clause 3.2 of the Code when the same item was approved by the MHRA as being in compliance with Regulations 3A(1) of the Advertising Regulations and Paragraph 4.3 of the Blue Guide. In addition, during the pre-vetting process, the MHRA provided clear direction in its letter of 20 May, 2009 about what to place on the sales aid (which had the same layout as the advertisement in issue) in order to prevent the implication of a wider indication. 'The product is indicated for diabetes for glycaemic control. You should ensure that the references to other actions such as BP effects are clearly separated from and subsidiary to the main indication so as not to suggest a wider indication than in the SPC'.

In response to this letter, Novo Nordisk created the current layout of several materials, including the advertisement at issue, in particular including the features described above, to ensure the additional benefits were separated from and subsidiary to the main indication. A revised version of the layout in this form was sent back to the MHRA which did not object to the layout (MHRA letter, 5 June 2009).

Novo Nordisk therefore denied that the advertisement was in breach of Clause 3.2 of the Code.

Novo Nordisk noted that the Panel considered that the claim 'Reductions in weight' was misleading, ambiguous and exaggerated and that it could not be substantiated for each Victoza dose (1.2mg or 1.8mg) or licensed combination. The Panel further stated that the amount of the weight loss was small and highlighted the weight gain data with liraglutide 1.2mg in combination with glimepiride. Furthermore, the Panel contended that health professionals needed to know the amount of weight loss in order to fully understand this benefit and that it should have been specified that not every patient would lose weight.

Novo Nordisk submitted that with respect to the charge that the claim was misleading, unsubstantiated and exaggerated, it reiterated its comments made in this regard in A1 above. As highlighted the only subpopulation which demonstrated clinically non-significant (0.23kg) weight gain in the LEAD programme was the 1.2mg Victoza group (in combination with glimepiride) from Marre *et al* (LEAD 1). All other patients in the phase 3a programme regardless of whether they were randomized to 1.2mg or 1.8mg Victoza (in combination with metformin, metformin and glimepiride or metformin and rosiglitazone) lost weight of between 1.0 and 2.8kg on average.

Novo Nordisk noted the Panel's comment that the amount of weight loss was small, but submitted that whilst numerically it might have been small, it was still a significant benefit. Furthermore, health professionals acknowledged the unfavourable impact of weight gain or the favourable effect of weight loss on cardiovascular risk which was particularly important in type 2 diabetics. Lean *et al*, (1990), highlighted the importance of weight loss (even a minimum of 1kg) in type 2 diabetes which was associated with improved survival. More generally, even 1kg of weight gain in adulthood might increase the risk of coronary heart disease by 3.1 – 5.7% in the general population depending on gender (Anderson *et al*, 2001) and the same paper also described the importance of 1kg weight loss from the perspective of different cardiovascular risk factors.

Additionally, Novo Nordisk submitted that an expectation that a medicine would work in every patient in order to make a claim relating to its effect was clinically unfounded, as discussed in A1 above. Health professionals had realistic expectations in the clinical setting and they therefore interpreted such claims realistically – ie that the claimed effect was shown in a statistically significant number of patients, but there was no guarantee that it would occur in all.

Whilst Clauses 7.2 and 7.4 of the Code and Regulations 3A(2) and (3) of the Advertising Regulations/Paragraph 4.3 of the Blue Guide were not entirely equivalent, Novo Nordisk noted that pre-vetting against such requirements took place.

On the basis of the above, Novo Nordisk disagreed with the Panel that the weight claim in the advertisement was in breach of Clauses 7.2, 7.4 and 7.10 of the Code.

Novo Nordisk noted that the Panel considered that the claim 'Reductions in systolic blood pressure' was also misleading, ambiguous, exaggerated and not capable of substantiation. Section 5.1 of the SPC stated that Victoza decreased the systolic blood pressure on average by 2.3 to 6.7mmHg from baseline. This magnitude of systolic blood pressure drop was clearly clinically significant. According to the Prospective Studies Collaboration (2002), which analyzed the relevance of age-specific blood pressure to cause-specific mortality in 61 prospective observational studies (12.7 million person-years), even 2mmHg lower usual systolic blood pressure would involve about 10% lower stroke mortality and 7% lower ischaemic heart disease mortality. The systolic blood pressure reduction was a consistent finding throughout the LEAD trials. Nauck *et al* (LEAD 2) and Russell-Jones (LEAD 5) the reduction was statistically significantly greater than with the active comparator, whilst in Zinman *et al* (LEAD 4) it was statistically significantly larger than with the placebo (in this trial there was no active comparator tested). The only trial where the reduction did not reach the level of statistical significance (vs active comparator) was Marre *et al* (LEAD 1), although the magnitude of the blood pressure drop (2.6-2.8mmHg) seemed to be clinically significant on the basis of the Prospective Studies Collaboration (2002).

Thus Novo Nordisk submitted that the systolic blood pressure reduction claim was capable of substantiation, it was neither misleading nor ambiguous and was not exaggerated. Whilst Clauses 7.2 and 7.4 of the Code and Regulations 3A(2) and (3) of the Advertising Regulations/ Paragraph 4.3 of the Blue Guide were not entirely equivalent, Novo Nordisk noted that pre-vetting against such requirements took place.

Novo Nordisk therefore did not agree with the rulings by the Panel that this was in breach of Clauses 7.2, 7.4 and 7.10 of the Code.

On the basis of the above appeals Novo Nordisk submitted that the advertisement complied with the spirit of the Code and did not breach any of the above cited clauses by the Panel. It could not therefore be said that high standards had not been maintained and Novo Nordisk therefore also disagreed with the Panel's ruling of a breach of Clause 9.1.

COMMENTS FROM LILLY

Lilly noted that in a letter of 20 May 2009 the MHRA had asked Novo Nordisk to 'justify the claim "Get to the roots of type 2 diabetes". This could imply that the treatment will cure the disease' and 2 which stated 'The product is indicated for diabetes for glycaemic control. You should ensure that the references to other actions such as BP effects are clearly separated from and subsidiary to the main indication so as not to suggest a wider indication than in the SPC', The MHRA's question appeared to reflect the very concerns outlined by Lilly in its complaint.

APPEAL BOARD RULING

The Appeal Board noted that the advertisement stated 'Once-daily Victoza, in combination with metformin and/or a sulphonylurea, impacts on multiple findings associated with type 2 diabetes providing from baseline' below which were four bullet points; the first was 'Reductions in HbA1c'

which referred to the indication for Victoza. The next three bullet points were then separated from the first by a space followed by the words 'And in addition:' The next three bullet points were: 'Reductions in weight'; 'Reductions in systolic blood pressure' and 'Improvements in beta-cell function'. The Appeal Board considered that the separation of the indication for Victoza ie, lowering blood glucose, from its additional benefits was sufficient. The Appeal Board considered that the advertisement was not inconsistent with the Victoza SPC and ruled no breach of Clause 3.2. The appeal on this point was successful.

The Appeal Board noted that the Victoza SPC stated that weight loss ranged 'from 1.0kg to 2.8kg'. The Appeal Board considered that the claim 'Reductions in weight' was not inconsistent with the available data and the Victoza SPC. Health professionals would not expect every patient to lose weight with Victoza. The Appeal Board did not consider that the claim was misleading or incapable of substantiation or exaggerated. The Appeal Board ruled no breach of Clauses 7.2, 7.4 and 7.10. The appeal on this point was successful.

The Appeal Board noted the claim 'Reductions in systolic blood pressure' was referenced to Marre *et al* (LEAD 1), Nauck *et al* (LEAD 2) and the SPC. Marre *et al* (LEAD 1) stated that although blood pressure decreased with Victoza 1.2mg and 1.8mg combined with glimepiride (2.6 – 2.8mmHg) the change was not significantly different from that observed with placebo or rosiglitazone. Nauck *et al* (LEAD 2) reported significant reductions in systolic blood pressure (2 – 3mmHg) for 1.2mg and 1.8mg Victoza plus metformin compared with the increase observed with the glimepiride plus metformin group. The Victoza SPC stated that over the duration of the studies Victoza decreased systolic blood pressure on average 2.3 to 6.7mmHg from baseline and compared to active comparator the decrease in systolic blood pressure was 1.9 to 4.5mmHg. The Appeal Board noted that even a small reduction in systolic blood pressure was considered to be clinically relevant. The Appeal Board considered that the claim 'Reductions in systolic blood pressure' was not inconsistent with the data and the Victoza SPC. The Appeal Board did not consider that the claim was misleading, exaggerated or incapable of substantiation. The Appeal Board ruled no breach of Clauses 7.2, 7.4 and 7.10. The appeal on this point was successful.

The Appeal Board noted its rulings above and considered that Novo Nordisk had not failed to maintain high standards. The Appeal Board ruled no breach of Clause 9.1. The appeal on this point was successful.

2 Reprint folders (UK/LR/0409/0085 and UK/LR/0609/0202)

The folders at issue were similar to each other; the front cover of each included the same claims and illustration as in the advertisement at issue in Point B1 above. One folder (UK/LR/0609/0202) additionally included the claim 'SMC [Scottish Medicines Consortium] Pending' on the front cover in a yellow box. The back cover included a list of references and the prescribing information.

The folders provided by Novo Nordisk were empty and there was no mention as to what was provided in the folders.

COMPLAINT

Lilly stated that its comments about the advertisement in Point B1 above applied to the front covers of the folders.

Lilly further alleged that the highlighted and prominent statement 'SMC Pending' was misleading. In itself the wording was, at best, meaningless however, Novo Nordisk's intent behind this was clear given the promotional context in which it was introduced. 'Pending' was synonymous with imminent, prospective, impending and had a very particular meaning in regulatory parlance as would be employed by organisations such as the SMC. In this regard, this statement clearly inferred that Victoza had been accepted for use within NHS Scotland pending formal ratification by the SMC. The SMC had stated that its decision on the acceptability of Victoza would be published on 7 December 2009. The claim was clearly misleading and undermined prescriber confidence in the pharmaceutical industry and patient safety. Lilly alleged a breach of Clauses 2, 7.2, 7.4, 7.10 and 9.6.

RESPONSE

Novo Nordisk referred to its response to Point B1 above and also to the correspondence from the MHRA of 3 June 2009 (a copy of which was provided), which provided approval of one of the folders (UK/LR/0409/0085).

Novo Nordisk disagreed that the statement 'SMC Pending' implied that would be approved by the SMC. The SMC was currently evaluating Victoza, and would publish its decision would on 7 December 2009. 'SMC pending' reflected the fact that Victoza was currently being reviewed by the SMC.

Novo Nordisk disagreed that this material was in breach as alleged by Lilly.

PANEL RULING

The Panel considered that its rulings at Point B1 above applied here. These rulings were appealed.

With regard to the phrase 'SMC Pending' the Panel noted that 'pending' could be variously defined as, *inter alia*, 'while waiting for', 'not yet decided, confirmed or finished' and 'imminent'. The Panel considered that the claim 'SMC Pending' strongly

implied that SMC approval was a formality or a matter of time rather than reflecting that Victoza was going through the SMC process. The Panel considered the claim was ambiguous and thus misleading. A breach of Clause 7.2 of the Code was ruled. The Panel considered that the fact that the SMC was actively considering the product was sufficient with regard to the requirement to provide substantiation and thus no breach of Clause 7.4 was ruled. The claim did not exaggerate the position nor was it a claim for a special merit. No breach of Clause 7.10 was ruled.

The Panel ruled no breach of Clause 9.6. Novo Nordisk had not reproduced an official document without permission.

The Panel did not consider that the use of the phrase 'SMC Pending' warranted a ruling of Clause 2 which was a sign of particular censure and reserved for such use.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that since the Panel considered that its rulings at Point B1 applied here, it repeated its comments and position set out in B1.

Novo Nordisk noted that in light of the breach accepted in respect of the phrase 'SMC Pending', reprint folder UK/LR/0609/0202 had been withdrawn.

COMMENTS BY LILLY

There were no comments from Lilly.

APPEAL BOARD RULING

The Appeal Board noted it comments and rulings in Point B1 above regarding the advertisement which it considered also applied here.

3 Leavepieces 'Do more than lower blood glucose' (UK/LR/0409/0079 and UK/LR/0609/0192)

The two leavepieces were similar to each other; page 1 of each was the same as the front cover of the reprint folders at issue in Point B2 above ie one had 'SMC Pending' (UK/LR/0609/0192) and one did not (UK/LR/0409/0079).

Page 2 of the leavepiece was headed 'Victoza + metformin effectively reduced HbA1c' and showed data adapted from Nauck *et al* (LEAD 2).

Page 3 was headed 'In addition: Victoza + metformin help patients achieve early weight loss' and was referenced to Nauck *et al* (LEAD 2) and Novo Nordisk data on file.

The subheading on Page 3 'Weight loss was seen at 2 weeks and totalled 2.6kg at 26 weeks compared with metformin + glimepiride (1kg weight gain at 26 weeks)' was referenced to Nauck *et al* (LEAD 2) and Novo Nordisk data on file. A graph of the data appeared beneath the subheading.

COMPLAINT

Lilly repeated its comments at Point B1 regarding page 1 of the leavepieces.

The heading on page 2 'Victoza + metformin effectively reduce HbA1c' was followed by 'Victoza + metformin provide significant reductions in HbA1c compared with metformin alone – with a low risk of hypoglycaemia' and referenced to Nauck *et al* LEAD 2. This was followed by a bar chart which compared the mean change from baseline HbA1c (8.4%) in patients previously treated with oral antidiabetic monotherapy at 26 weeks. The bar chart depicted a reduction from baseline of 1.25% for Victoza 1.2mg in combination with metformin 2000mg, a reduction of 0.38% for metformin 2000mg and a reduction of 1.15% for glimepiride 4mg combined with metformin 2000mg. Statistical significance of $p<0.0001$ vs metformin 2000mg was assigned with respect to the mean reduction from baseline in HbA1c of 1.25% for Victoza 1.2mg in combination with metformin 2000mg.

Lilly alleged that the claimed reduction in HbA1c by 1.25% was only true for the subgroup of patients in Nauck *et al* (LEAD 2) that were previously treated with monotherapy. This subgroup comprised only 35% of the total study population. For all patients treated with Victoza, however, this statement was incorrect and misleading. Table 2 in Section 5.1 of the Victoza SPC, indicated that the mean reduction in baseline in HbA1c for liraglutide 1.2mg in combination with metformin 2000mg was 0.97% and not 1.25%. The 0.97% reduction was also consistent with the results reported for the total population in Nauck *et al* (LEAD 2). The claim in question was therefore misleading, incorrect and inconsistent with the SPC. The chart also misled by omission and association with reference to the results reported for glimepiride 4mg combined with metformin 2000mg; there was no indication that the comparison with the Victoza 1.2mg arm was not statistically significant, albeit this was pre-specified in the statistical analysis plan for the study.

The layout of the chart invited a direct comparison of the relative efficacy of Victoza, metformin and glimepiride with regard to reductions in HbA1c from baseline and misleadingly indicated a superior benefit associated with Victoza 1.2mg compared with glimepiride 4mg. Nauck *et al* (LEAD 2) clearly stated that no such inference could be drawn given that there was no difference in the HbA1c reduction between Victoza and glimepiride. The reader was also misled by omission of the fact that the HbA1c reduction in two-thirds of the patients in Nauck *et al* (LEAD 2) was -0.68% for Victoza 1.2 mg and 0.78% for glimepiride 4mg. The reader was also misled with respect to the selective use of data from Nauck *et al* (LEAD 2). Omission of the comparative results for Victoza 1.8mg misled the reader regarding the

comparative efficacy of this particular dose vs Victoza 1.2mg and glimepiride 4mg. Given that the mean change from baseline in HbA1c for Victoza 1.8mg in combination with metformin 2000mg was 1%, Lilly suspected this was a convenient and commercially driven omission designed to avoid the obvious conclusion that the higher dose of Victoza was no more efficacious than Victoza or glimepiride 4mg. Importantly, the claims were not substantiated by Nauck *et al* (LEAD 2) given that neither this study nor any other published reported pre-specified a direct comparison of Victoza vs metformin monotherapy as was stated on this page. Thus the claims 'Victoza + metformin provide significant reductions in HbA1c compared with metformin alone ...' and 'p<0.0001 vs. metformin' were factually incorrect and misleading. The comparison was not with metformin monotherapy but with a placebo as clearly highlighted in the Victoza SPC and Nauck *et al* (LEAD 2).

The first bullet point beneath the chart on page 2 stated in emboldened font that 'Some patients experienced even greater reductions in HbA1c – patients with baseline HbA1c levels above 9.5% experienced a 2.74% reduction in HbA1c with Victoza 1.2mg in combination with metformin'. The claim was referenced to Nauck and Marre (2009).

Lilly alleged that this claim was misleading as it relied on cherry-picked and incorrect data. Nauck and Marre, a post-hoc analysis of two phase III randomised control clinical trials, LEAD 1 and LEAD 2 was cited in support of the claim. The analysis, involving 386 subjects, included only the 1.8mg dosage of Victoza and not the 1.2mg dosage as was asserted. The claim was therefore not only factually inconsistent with the citation but it also did not represent the balance of evidence as represented by the five double blind, randomised controlled trials conducted in 3,978 patients to evaluate the effects of Victoza 1.2mg on glycaemic control. Indeed, the authors stated that the:

> 'Glycosylated haemoglobin reductions with liraglutide, placebo and the active comparator in the subset of patients previously on OAD [oral antidiabetic therapy] monotherapy were larger than previously published results observed in the total patient population, which included patients on previous OAD monotherapy and combination therapy. This may reflect the fact that patients in the current analysis had less advanced diabetes than the total OAD therapy populations examined in the earlier studies'.

Notwithstanding that this claim was not substantiated by the reference, the incredibly selective and unbalanced aspect of this claim was evidenced by the very small number of LEAD 2 subjects (n = 16) with particularly high baseline HbA1c previously on oral monotherapy upon which it relied for apparent substantiation. The authors stated that 'It is difficult to compare HbA1c reductions across unrelated trials because of differences in patient populations and protocols' thereby highlighting the significant limitations of the data in support of any such claim. In inter-company dialogue Novo Nordisk asserted that this claim was fully substantiated and not incorrect; notwithstanding this, Novo Nordisk had agreed to remove it from the leavepiece but did not confirm that this misleading leavepiece, as well as all other Victoza materials containing this claim, had been withdrawn from use with immediate effect, as per Lilly's request.

The next bullet points on page 2 of the leavepiece referred to hypoglycaemic events:

> 'Statistically, fewer minor hypoglycaemic events were observed with Victoza in combination with metformin compared with metformin in combination with glimepiride (p<0.001)' referenced to Nauck *et al* (LEAD 2).

and

> 'No major hypoglycaemic events were observed with Victoza in combination with metformin [referenced to Nauck *et al* (LEAD 2)]. In a separate study, no major hypoglycaemic events were observed with Victoza in combination with metformin and a thiazolidinedione (TZD) [referenced to Zinman *et al* 2009 (LEAD 4)]'.

Lilly alleged that the focus of the classification of hypoglycaemic events with respect to severity (ie minor and major events) and incidence (ie low risk, fewer, no events) was misleading and unbalanced as it implied that hypoglycaemia did not occur commonly and was of no clinical consequence to either patients or prescribers. The latter was also evidenced by the third bullet point which stated 'In a separate study, no major hypoglycaemic events were observed with Victoza in combination with metformin and a thiazolidinedione (TZD)'. This was inconsistent with the Victoza SPC which stated that hypoglycaemia was common and very common with respect to Victoza when combined with glimepiride, metformin and glimepiride and metformin and rosiglitazone; this was irresponsible and potentially compromised patient safety.

Lilly alleged that page 3 of the leavepiece further misled with regard to the licensed indication of Victoza by promoting it as an anti-obesity medicine. The heading 'In addition: Victoza + metformin help patients achieve early weight loss' referred to 'Victoza' which invited the reader to consider that the weight reduction was applicable to all doses of liraglutide. This impression was further emphasised in the sub-heading which emphasised the early reduction in 'weight loss seen at 2 weeks' compared to metformin and glimepiride 4mg. It was only in the graph which followed that specific reference, in very small font, was made to Victoza 1.2mg in combination with metformin. Given the prominence of the unqualified reference to 'Victoza' in the headline, the reader was misled to believe that the magnitude and timing of the weight reduction

reported in the graph was applicable to all doses of liraglutide when combined with metformin, glimepiride and rosiglitazone. Thus the weight reduction reported on this page for Victoza 1.2mg was selective, did not represent the balance of evidence and was inconsistent with the SPC which stated that 'Victoza in combination with metformin, metformin and glimepiride or metformin and rosiglitazone was associated with sustained weight reduction over the duration of studies in a range from 1.0kg to 2.8kg'.

The prominence given to discussion of the weight reduction was skewed and inconsistent with the primary efficacy endpoint of the cited study which was to assess the mean change from baseline in HbA1c at 26 weeks and not weight reduction, as implied. In the absence of p-values, reporting 'early' weight reduction after two weeks implied statistical significance to this observation; this was misleading and inconsistent with the statistical analysis plan.

In the absence of any indication of the baseline body weight and BMI, by which the implied clinical and statistical significance of the reductions referred to could be assessed, the claims about weight reduction misled readers by omission and exaggerated the results. Lilly noted that the Victoza SPC stated that 'Larger weight reduction was observed with increasing body mass index (BMI) at baseline'.

The improvements in HbA1c discussed on page 2 were appropriately contextualised with references to the severity and incidence of hypoglycaemia. However, given that the weight loss associated with liraglutide was attributed to delayed gastric emptying, it would have been equally appropriate to inform readers of the incidence of nausea, diarrhoea, vomiting, dyspepsia which variously occurred commonly or very commonly with liraglutide. This omission misled by omission and potentially compromised patient safety.

At the bottom of page 3 it was stated 'Weight loss with Victoza provides reductions in visceral fat' and 'Visceral fat was reduced by 13% to 16% in patients treated with Victoza vs. 8% in placebo-treated patients' reference to Jendle *et al* (2008). In the absence of percentages indicating the proportion of visceral fat at baseline, and the clarification that the comparison was relative to abdominal subcutaneous adipose tissue, as opposed to lean body tissue or total fat, the clinical significance and relevance of this observation was questionable and therefore misled the reader and exaggerated the facts. The visceral tissue was only assessed with reference to Nauck *et al* (LEAD 2) which looked at liraglutide in combination with metformin vs placebo or glimepiride 4mg. Thus the claim was misleading as it invited relevance of this observation to liraglutide when combined with other oral antidiabetics such as rosiglitazone.

Lilly stated that all of the concerns outlined above also related to item number UK/LR/0609/0192. With respect to the latter, the concerns outlined in point B2 were also relevant.

Lilly alleged that the leavepiece was in breach of Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.8, 7.10, 8.1 and 9.1 of the Code.

RESPONSE

Novo Nordisk referred to its response to Point A2 above.

Novo Nordisk submitted that the leavepiece, focused, (as described in the headline), on once daily Victoza 1.2mg in combination with metformin. As referenced, this clinical situation was examined in Nauck *et al* (LEAD 2). The reduction in HbA1c in the subgroup of patients receiving prior oral therapy was clearly stated in Nauck *et al* (LEAD 2) with a detailed description of the effect according to previous treatment.

Nauck *et al* (LEAD 2) was included in this leavepiece as it was the only LEAD study that investigated the combination of Victoza and only metformin. The inclusion of this data, therefore, aligned this leavepiece with the published Nathan *et al* (2009) guidelines.

The claim regarding the reduction of HbA1c by 1.25% in patients receiving prior oral monotherapy reflected 'real-life' clinical prescribing, where patients would receive liraglutide as 'add-on' treatment to one oral antidiabetic medicine. This was consistent with the treatment sequence as recommended in the global guidelines, Nathan *et al*. Novo Nordisk, therefore, disputed that the statement was misleading, or factually incorrect. The asterisk presented in the -1.25% bar for liraglutide 1.2mg clearly indicated that this was $p<0.0001$ vs metformin. There was no significant difference to glimepiride and therefore, Novo Nordisk maintained that no further symbols were needed to denote this. Novo Nordisk did not believe that the absence of a symbol to denote non-significance was entirely appropriate and did not mislead by omission.

Furthermore, Novo Nordisk disputed that the layout of the graph indicated a superior benefit associated with 1.2mg liraglutide compared with glimepiride 4mg, for the reasons stated above.

As mentioned above, patients receiving previous monotherapy (one third) reflected real-life clinical prescribing in which liraglutide would be 'added on' to one oral antidiabetic medicine. The subgroup of patients (two thirds) receiving combination oral antidiabetic therapy prior to trial had one of two oral antidiabetics removed, which was then substituted with liraglutide. This scenario did not reflect real-life clinical prescribing and, therefore, was not relevant for discussion in this leavepiece. Novo Nordisk, therefore, disputed that the reader was misled by omission.

The standard Victoza treatment dose was 1.2mg;

some patients were expected to benefit from an increase in dose to 1.8mg. In this leavepiece, Novo Nordisk promoted the 1.2mg standard dose only, in accordance with the licensed indications. Novo Nordisk therefore disputed that this was convenient or commercially-driven omission as alleged.

Patients randomised to the placebo arm of Nauck *et al* (LEAD 2) received metformin monotherapy, therefore, the claim 'Victoza + metformin provide significant reductions in HbA1c compared with metformin alone' and 'p<0.0001 vs. metformin' were substantiated by Nauck *et al* (LEAD 2).

With regard to the claim '… patients with baseline HbA1c levels of above 9.5% experienced a 2.74% reduction in HbA1c with Victoza in combination with metformin', Novo Nordisk disputed that this was incorrect data as the claim was fully substantiated by the cited reference, Nauck and Marre 2009. However, Novo Nordisk had agreed to remove this statement in this UK leavepiece.

In response to the concern raised by Lilly with regard to the classification of hypoglycaemia events, the SPC stated:

'Most episodes of confirmed hypoglycaemia in clinical studies were minor. No episodes of major hypoglycaemia were observed in the study with Victoza used as monotherapy. **Major hypoglycaemia may occur** uncommonly and has primarily been observed when Victoza is combined with a sulphonylurea (0.02 events/subject year). **Very few episodes** (0.001 events/subject year) **were observed with administration of Victoza in combination with oral antidiabetics other than sulphonylureas**.' (emphasis added).

As such, the language used in this leavepiece with regard to hypoglycaemia was appropriate and consistent with the SPC. Novo Nordisk did not believe that the leavepiece implied that hypoglycaemic events were of no clinical consequence to patients or prescribers.

With regard to page 3 of the leavepiece Novo Nordisk stated that the allegation that it referred to only Victoza in this leavepiece was incorrect. The heading actually stated 'In addition: Victoza + metformin help patients achieve early weight loss' and was appropriately referenced to Nauck *et al* (LEAD 2). In this study, weight reduction was applicable to all doses of liraglutide in combination with metformin. Novo Nordisk believed the heading was substantiated and was clearly referenced.

Novo Nordisk was confused by the allegation that given the prominence of the unqualified reference to 'Victoza' in the heading, the reader was misled to believe that the magnitude and timing of the weight reduction reported in the graph was applicable to all doses of liraglutide when combined with metformin and glimepiride and rosiglitazone. As stated above, the heading on page 3 stated 'In addition: Victoza + metformin help patients achieve early weight loss' and was appropriately referenced to Nauck *et al* (LEAD 2) which confirmed that weight loss was associated with all doses of liraglutide when used in combination with metformin.

Novo Nordisk disputed that presenting weight reduction for the 1.2mg Victoza dose only was selective. The Victoza SPC suggested that the standard treatment dose was 1.2mg. As such, in this leavepiece, Novo Nordisk had promoted the 1.2mg dose, in accordance with the licensed indications.

If it were being selective in the dose presented, it could have used the data about the non-standard 1.8mg dose where a weight reduction of 2.8kg was shown, rather than the 2.6kg weight reduction presented. Novo Nordisk was unclear why Lilly alleged it was being selective, given the above and the fact that the data presented on weight reduction fell within the range stated in the SPC.

Novo Nordisk did not agree that the prominence of the weight reduction results on page 3 skewed the endpoint of the study. The inclusion of data on weight reduction appeared on page 3 following discussion regarding the primary efficacy endpoint of this study, namely the reduction in HbA1c on page 2.

Novo Nordisk had not included any mention of statistical significance in relation to the claim that early weight loss was seen. Therefore, Novo Nordisk disputed that the absence of a statement claiming statistical significance could actually imply that statistical significance existed.

With regard to the absence of any indication of the baseline body weight and BMI, Novo Nordisk noted that Nauck *et al* (LEAD 2) did not involve a specific patient population with type 2 diabetes but recruited typical type 2 diabetics. Thus Novo Nordisk believed that any clinician that cared for such people could easily evaluate and interpret the clinical importance of the magnitude of the weight loss indicated on the graph without specifying the baseline values of the above parameters.

Novo Nordisk submitted that it would not be appropriate in the leavepiece to go into detail regarding adverse events associated with delayed gastric emptying, since the mechanisms of weight loss were not referred to, and were beyond the scope of the leavepiece. Novo Nordisk further disputed that this omission potentially compromised patient safety, particularly given that the prescribing information which set out the warnings and precautions for use was included.

Novo Nordisk did not agree that the claim stated at the bottom of page 3 'Weight loss with Victoza provides reductions in visceral fat' suggested that this observation was relevant to combinations with other oral antidiabetic medicines rather than only when Victoza was combined with metformin, given the bold large font heading at the top of this page clearly stated the observation was when Victoza

was used with metformin.

Novo Nordisk did not believe that the absence of percentages indicating the proportion of visceral fat at baseline in study subjects was misleading. The claim simply emphasized the clinically important change in visceral fat and put it in context with the observed change with placebo. In this regard the baseline percentage of visceral fat would not add any significant additional information.

The reduction in visceral fat, regardless of whether it was compared with abdominal subcutaneous fat, lean body tissue or total fat was of clinical significance to patients and prescribers and therefore Novo Nordisk believed that its inclusion was entirely justified.

As Novo Nordisk stated in inter-company dialogue, the statement 'Some patients experienced even greater reduction in HbA1c – patients with baseline HbA1c levels of 9.5% experienced a 2.74% reduction in HbA1c with Victoza 1.2mg in combination with metformin' had been removed from the promotional materials. During inter-company dialogue the original pieces (refs UK/LR/0409/0079 and UK/LR/0609/0192) were no longer in use (both pieces were formally withdrawn on 9 September 2008 sic) and had now been replaced with new materials (UK/LR/0809/0380 and UK/LR/0809/0381). Copies of the original and the new pieces were provided.

Given the above, Novo Nordisk denied that the material was in breach as alleged.

PANEL RULING

The Panel considered that its rulings at Point B1 above applied here. These rulings were appealed. With regard to the phrase 'SMC Pending' the Panel considered its ruling at point B2 above applied here.

Turning to page 2 of the leavepiece the Panel noted that Nauck *et al* (LEAD 2) assessed the efficacy and safety of adding Victoza to metformin compared with the addition of placebo or glimepiride to metformin in subjects previously treated with oral antidiabetic (OAD) therapy. The majority of patients were treated with two OADs before the study. The authors stated that mean HbA1c values for the overall population decreased by 1.0 ± 0.1% for both the 1.2mg and 1.8mg liraglutide groups and the glimepiride group. The bar chart at issue, however, was for the subgroup of patients whose previous OAD therapy was monotherapy. The small print next to the bar chart in the leavepiece stated that it related to a subgroup analysis. The page heading and sub-heading, however, did not refer to previous OAD monotherapy. The overall result and the result for those who had combination OAD therapy prior to the study (these reductions being 0.68% for liraglutide 1.2mg, 0.71% for liraglutide 1.8mg and 0.78% for glimepiride 4mg) showed less of a difference between liraglutide and glimepiride than the result for those who had OAD monotherapy as previous treatment which was the only data in the bar chart in the leavepiece.

The Panel did not consider that the claim in question 'Victoza + metformin provide significant reductions in HbA1c compared with metformin alone …' was misleading in that Nauck *et al* (LEAD 2) stated that HbA1c values were significantly reduced in all liraglutide groups v placebo ($p<0001$) with mean decreases of 1.0% for 1.2mg and 1.8mg of liraglutide and glimepiride and an increase of 0.1% for placebo. No breach of Clause 7.2 was ruled. The Panel noted that Nauck *et al* (LEAD 2) compared various doses of liraglutide plus metformin with placebo plus metformin or metformin plus glimepiride. The explanation '$p<0.0001$ versus metformin' was confusing in that every combination included metformin. A breach of Clause 7.2 was ruled in this regard.

The Panel considered the chart was misleading in that only the results for patients pretreated with OAD monotherapy were shown. Thus the Panel ruled a breach of Clauses 7.3, 7.8 and 7.10 of the Code. The Panel considered that the asterisk by the liraglutide data would be assumed to indicate a statistically significant difference. No explanation was given. The lack of the asterisk by the glimepiride/metformin data could be read as implying there was a difference between this and Victoza 1.2mg plus metformin with regard to HbA1c changes from baseline and when considering the overall results rather than the results for patients previously treated with monotherapy; this was not so. The Panel could not find any statistical details regarding this in Nauck *et al* (LEAD 2) but there was a general statement that the HbA1c profiles of subjects stratified by prestudy therapy, monotherapy or combination therapy were similar in appearance to those of the overall population and that 'the baseline and end of study mean [HbA1c] values in the monotherapy group were slightly less than those in the combination therapy group, and the resulting change-from-baseline decreases appeared to be slightly greater in the monotherapy group than in the combination therapy group'. In that regard the Panel considered that the data had been cherry-picked to show the results which demonstrated the largest positive difference for Victoza. A further breach of Clause 7.3 and 7.8 of the Code was ruled. The impression could not be substantiated and a breach of Clause 7.4 was ruled. The Panel considered that the positioning and presentation of the claim '$p<0.0001$ versus metformin' above the glimepiride reinforced the misleading impression of a statistically significant difference between the Victoza + metformin and the glimepiride + metformin data. This was misleading and a breach of Clause 7.2 was ruled.

The presentation of the data was inconsistent with the SPC and a breach of Clause 3.2 was ruled. This ruling was appealed.

The Panel noted that Novo Nordisk had agreed to remove the claim 'Some patients experienced even greater reductions in HbA1c – patients with baseline

HbA1c levels above 9.5% experienced a 2.74 reduction in HbA1c with Victoza 1.2mg in combination with metformin' from the leavepiece. The Panel was unsure whether the claim appeared in any other promotional material and this point had not been addressed in Novo Nordisk's response, either to Lilly or to the Authority. Nonetheless, it appeared that inter-company dialogue had been successful and thus the Director decided that the Panel should not consider the allegation about this claim.

The Panel noted that the SPC stated that hypoglycaemia was common and very common when Victoza was used in combination with a sulphonylurea. Major hypoglycaemia had primarily been observed when combined with a sulphonylurea. The SPC listed hypoglycaemia as common with liraglutide plus metformin plus rosiglitazone and liraglutide plus glimepiride. Hypoglycaemia was very common with liraglutide plus metformin and glimepiride.

The Panel noted that the claim 'Statistically, fewer minor hypoglycaemic events were observed with Victoza in combination with metformin compared to metformin in combination with glimepiride ($p<0.001$), referenced to Nauck *et al*, (LEAD 2) reflected the evidence from that trial and also the information in the SPC where no frequency of hypoglycaemia was stated for liraglutide with metformin. In that regard the Panel did not consider that the claim was misleading. No breach of Clause 7.2 was ruled. However, in the Panel's view, the claim 'In a separate study, no major hypoglycaemic events were observed with Victoza in combination with metformin and a thiazolidinedione (TZD)' sought to minimize a clinician's concerns regarding the occurrence of hypoglycaemia in this treatment group. The SPC listed hypoglycaemia as common in patients being so treated. Omission of this data, given the inclusion of data about major hypoglycaemia, was misleading. A breach of Clause 7.2 was ruled.

The Panel noted that page 3 presented the weight loss data for Victoza 1.2mg in combination with metformin although, as before, the heading and subheading did not make it clear that the results were for one dose of Victoza only. The Panel noted that the weight loss shown for Victoza plus metformin (2.6kg) was within the range stated in the general comment in the SPC that sustained weight reduction over the duration of studies ranged between 1.0kg to 2.8kg (both 1.2mg and 1.8mg Victoza doses). The data was an accurate reflection of Nauck *et al* (LEAD 2) and it clearly related to Victoza combined with metformin. No breach of Clauses 7.2 and 7.3 was ruled.

The Panel did not consider the presentation of the weight loss data was skewed and inconsistent with the fact that the primary efficacy endpoint of the study was to assess changes in HbA1c. The Panel noted its comments in this regard in Point B1 above.

The Panel did not consider that the reference to early weight loss and the absence of p values in this regard implied a statistically significant difference as alleged. The Panel ruled no breach of Clause 7.2 of the Code.

The Panel considered that although it would have been helpful to have an indication of baseline body weight the absence of this data was not necessarily misleading. No breach of Clause 7.2 was ruled.

The Panel did not consider that the omission of data regarding the incidence of nausea, diarrhoea, vomiting, dyspepsia from this page was misleading as alleged. No breach of Clauses 7.2 and 7.10 was ruled.

The Panel noted that Jendle *et al* was entitled 'The reduction in bodyweight with liraglutide, a once-daily human GLP-1 analogue for type 2 diabetes, primarily comes from fat tissue and the fat tissue lost is predominately visceral fat'. The data was preplanned substudies of data from LEAD 2 and LEAD 3. The differences between treatment groups for the changes from baseline were statistically significant for liraglutide 1.2mg and 1.8mg each vs glimepiride for visceral adipose tissue ($p<0.05$).

The Panel did not consider that the visceral fat data in the leavepiece in the absence of clarification that the comparison was relative to abdominal subcutaneous adipose tissue was in itself misleading or that the omission of details of baseline values was misleading or exaggerated the facts as alleged. No breach of Clauses 7.2 and 7.10 was ruled.

The Jendle *et al* data was relevant to the page in the leavepiece which referred to a glimepiride comparison. There was no mention of rosiglitazone. Thus the Panel did not consider that readers would infer that the visceral fat data was relevant in that regard and the Panel did not consider the leavepiece was disparaging. Lilly had not made a detailed allegation in this regard. No breach of Clause 8.1 was ruled.

The Panel considered that overall the leavepieces failed to maintain high standards and a breach of Clause 9.1 was ruled. With regard to Clause 2 the Panel did not consider that the leavepieces warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that since the Panel considered that its rulings at Point B1 applied here, it repeated its position set out in B1.

In addition, as to the specific rulings related to these pieces, the Panel considered that the explanation of statistical significance that appeared in the graph on page 2 of the leavepieces was misleading. Novo Nordisk accepted this ruling and pointed out that

these materials had been amended recently to provide clear information to the reader and highlight separately the level of statistical significance relating to the comparison between liraglutide 1.2mg plus metformin/glimepiride plus metformin vs placebo plus metformin. In light of this and other rulings accepted, these leavepieces would be withdrawn.

However, Novo Nordisk appealed against the alleged breach of Clause 3.2 when the Panel decided that the presentation of the data was inconsistent with the SPC. The graph contained results from a subgroup of Nauck *et al* (LEAD 2) which was covered by the SPC. Although the HbA1c improvement in this subgroup could not be found specifically in the SPC, the observed results were consistent with the results revealed in the overall study population. The subgroup-specific HbA1c improvement was published in LEAD 2.

Novo Nordisk submitted that it was inappropriate and unjust for the Panel to rule a breach of Clause 3.2 of the Code when the same item was approved by the MHRA as being in compliance with Regulation 3A(1) of the Advertising Regulations and Paragraph 4.3 of the Blue Guide.

COMMENTS FROM LILLY

There were no comments from Lilly.

APPEAL BOARD RULING

The Appeal Board noted its comments and rulings in Point B1 above regarding the advertisement which it considered also applied here.

The Appeal Board noted that the chart had been ruled to be misleading. However, the Appeal Board considered that the patients in the study were treated in accordance with the licensed indication for Victoza. The Appeal Board did not consider that the presentation of the data was inconsistent with the Victoza SPC. The Appeal Board ruled no breach of Clause 3.2. The appeal on this point was successful.

4 Leavepieces 'Get to the roots of the data on Victoza' (UK/LR/0409/0080 and UK/LR/0609/0201)

The two leavepieces were similar to each other. Page 1, the front cover, of one of the leavepieces included the statement 'SMC Pending' (UK/LR/0609/0201) similar to the clinical folder in point B2 and one of the leavepieces in point B3. The other leavepiece (UK/LR/0409/0080) did not include this phrase.

The front cover of the leavepieces was headed 'Get to the roots of the data on Victoza' followed by the details of the indication.

Pages 2 and 3 formed a double page spread headed 'A strong spread of evidence supports Victoza' beneath which appeared detailed data Nauck *et al* (LEAD 2), Marre *et al* 2009 (LEAD 1) and Zinman *et al* (LEAD 4).

The data was divided into the following three sections: Victoza or glimepiride added on to metformin where data from Nauck *et al* (LEAD 2) and data on file were presented; Victoza or rosiglitazone added on to glimepiride where data from Marre *et al* (LEAD 1) and data on file were presented and Victoza or placebo added on to metformin + rosiglitazone where data from Zinman *et al* (LEAD 4) and data on file were presented. The leavepiece gave certain HbA1c data, weight change data, systolic blood pressure change data and hypoglycaemia data for each of the Victoza combinations.

Page 4, the back cover, of the leavepiece included the boxed text at issue in the advertisement at Point B1:

'Once-daily Victoza, in combination with metformin and/or a sulphonylurea, impacts on multiple factors associated with type 2 diabetes providing from baseline

- Reductions in HbA1c

And in addition

- Reductions in weight
- Reductions in systolic blood pressure
- Improvements in beta-cell function.'

COMPLAINT

Lilly referred to the comments made about the advertisement in Point B1 above which it alleged applied to the cover of the leavepiece.

Lilly further alleged that, with regard to pages 2 and 3 and as outlined previously, the discussion of weight and systolic blood pressure reduction misled the reader to consider liraglutide as an anti-obesity agent and an antihypertensive. Further, the reader could not assess the clinical significance of any reduction in body weight or systolic blood pressure in a meaningful manner without reference to baseline qualifications; this was misleading by omission and exaggerated the facts.

As outlined previously, the discussion of major and minor hypoglycaemic events, in the context of promotional materials, was misleading and potentially compromised patient safety as it understated the importance of any such event to the patient and their quality of life.

The table presented a 6.7mmHg reduction of systolic blood pressure associated with liraglutide 1.2mg and rosiglitazone plus metformin compared with placebo (rosiglitazone plus metformin) referenced to Zinman *et al* 2009 (LEAD 4). Lilly alleged that the figure of -6.7mmHg was incorrect

and therefore misleading. The results section of Zinman *et al* (LEAD 4) included confidence intervals which were omitted from the leavepiece. The inclusion of the confidence intervals would have provided the reader with important and clinically relevant qualification to the absolute numbers presented. Further, for the statistical comparison of the placebo and liraglutide groups, Zinman *et al* (LEAD 4) reported that the placebo-corrected difference in the blood pressure reduction in the 1.2mg liraglutide group was not 6.7mmHg, as stated in the leavepiece, but rather a reduction of 5.6mmHg.

Lilly referred to its comments about the advertisement in Point B1 above which it alleged applied to the similar claim on page 4 of the leavepiece.

Lilly alleged that all of the concerns outlined above also related to item number UK/LR/0609/0201. With respect to the latter, the concerns outlined in point B2 above were also relevant.

For the reasons outlined above Lilly alleged that this leavepiece was in breach of Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.8, 7.10, 8.1 and 9.1 of the Code.

RESPONSE

Novo Nordisk referred to its comments with regard to the advertisement at Point B1 in relation to the page 1 of the leavepiece.

With regard to pages 2 and 3 Novo Nordisk submitted that the data about weight and/or blood pressure reductions did not imply that Victoza had an anti-obesity or antihypertensive indication. The indication for Victoza for the treatment of adult type 2 diabetics to achieve glycaemic control was quite clearly stated on the front of the leavepiece and in the prescribing information on page 4. Further, Novo Nordisk did not believe that the overall content emphasized weight reduction as an end point and as such did not allow Victoza's licensed indication to be misinterpreted.

Novo Nordisk referred to its previous comments regarding the discussion concerning major and minor hypoglycaemic events in the context of promotional materials.

Novo Nordisk disagreed that the reduction in blood pressure of 6.7mmHg with liraglutide 1.2mg and 5.6mmHg with liraglutide 1.8mg presented in the table was incorrect. These statements were neither incorrect nor misleading and, since there were no errors reported at all in the table, the inclusion of confidence intervals would be entirely inappropriate. Indeed all the data presented could have confidence intervals included but Novo Nordisk did not believe this was appropriate in this case. The systolic blood pressure values in the table were, as quite clearly stated in the column heading 'Mean SBP change from baseline (mmHg)' (emphasis added) and not differences vs placebo. The p-values clearly referred to the differences vs placebo (since it was only on these ANCOVA model values that the statistics were performed) and this was, again, clearly stated in the table. The placebo-corrected reduction in systolic blood pressure from Zinman *et al* was indeed 5.6mmHg but this was not referred to at all in the table (as the values in the table were mean changes from baseline) and so this was also not incorrect.

With regard to page 4 Novo Nordisk referred to its comments in Point B1 regarding the visual and the advertisement UK/LR/0609/0087.

Taking into account the above comments, Novo Nordisk disagreed that the leavepieces were in breach as alleged.

PANEL RULING

With regard to the front page the Panel did not consider that the allegations in Point B1 were entirely relevant given that the leavepiece now at issue had a different claim to that in the advertisement at issue in Point B1 above. The only relevant allegation related to the use of the lollipop tree. The Panel did not consider that the combination of the lollipop tree and the claim on the leavepiece 'Get to the roots of the data on Victoza' implied that Victoza could uproot type 2 diabetes and eliminate the illness. The Panel considered that its ruling of no breach of Clauses 3.2, 7.2, 7.4 and 7.8 at Point B1 also applied here.

The Panel noted that the indication for Victoza was given on the front cover of the leavepiece.

Pages 2 and 3 did not distinguish between the licensed indication and the benefits set out in Section 5.1 of the Victoza SPC. In this regard the Panel noted relevant comments in point A1 above. The data on pages 2 and 3 of the leavepiece appeared beneath the heading 'A strong spread of evidence supports Victoza'. In that regard the benefits of therapy had not been separated from or placed subsidiary to the main indication. A wider indication was implied. On balance the Panel considered that the data on pages 2 and 3 were presented in a misleading manner in that it appeared all the data was covered by the indication for Victoza and this was not so. A breach of Clauses 7.2 and 7.3 was ruled. The Panel did not consider that the data, in effect, promoted Victoza for unlicensed indications and thus no breach of Clause 3.2 was ruled.

With regard to the absence of information about baseline measurements the Panel considered that as all the data was presented and much of it was included in the SPC the absence of information about baseline values was not in itself misleading. P values were included or 'N/S'. No breach of Clauses 7.2 and 7.3 was ruled in this regard.

With regard to the hypoglycaemia data the Panel noted that in a column of data recording the events

per subject year, zero events were recorded for all doses of Victoza except Victoza 1.8mg combined with glimepiride (0.009 events/subject year). The Victoza SPC did not, in a table of adverse reactions, differentiate between episodes of major and minor hypoglycaemia. However the SPC stated that hypoglycaemia was common and very common when Victoza was used in combination with a sulphonylurea. Major hypoglycaemia had primarily been observed when combined with a sulphonylurea. The SPC further stated that most episodes of confirmed hypoglycaemia in clinical studies were minor. Major hypoglycaemia might occur uncommonly and had primarily been observed when Victoza was combined with a sulphonylurea (0.02 events/subject year). Very few episodes (0.001 events/subject year) were observed with administration of Victoza in combination with oral antidiabetics other than sulphonylureas. The Panel thus did not consider that the leavepiece accurately reflected the balance of evidence as stated in the SPC with regard to major hypoglycaemic events. A breach of Clauses 7.2 and 7.3 was ruled.

With regard to the presentation of the reduction of 6.7mmHg in systolic blood pressure for the combination of Victoza 1.2mg with metformin and rosiglitazone the Panel noted that no confidence intervals were included anywhere in the table. For each of the three combinations placebo data was given and in this instance there was a reduction of 1.1mmHg for placebo. Readers could thus easily calculate that the placebo corrected blood pressure reduction was 5.6mmHg. The Panel considered that although the table presented complex data which would need to be read carefully to be understood it was not misleading per se to omit the baseline data as alleged by Lilly. No breach of Clauses 7.2 and 7.3 was ruled. The data was not exaggerated in that regard. No breach of Clause 7.10 was ruled.

With regard to page 4 the Panel considered that this was different to the advertisement in Point B1 above. Although the wording of the claim:

'Once-daily Victoza, in combination with metformin and/or a sulphonylurea, impacts on multiple factors associated with type 2 diabetes providing from baseline

- Reductions in HbA1c

And in addition

- Reductions in weight
- Reductions in systolic blood pressure
- Improvements in beta-cell function.'

was the same unlike the advertisement at issue in Point B1 it did not appear beneath the claim 'Do more than lower blood glucose'. In the leavepiece now at issue the claim appeared on page 4 following pages detailing the indication and a presentation of detailed data. However the Panel still considered that the claim on Page 4 as a summary of the preceding data was not acceptable and its rulings in Point B1 regarding this claim also applied. These rulings were appealed.

The Panel considered its ruling regarding the use of the phrase 'SMC pending' in point B2 also applied here. The Panel did not consider that the leavepiece was disparaging and no breach of Clause 8.1 was ruled.

In relation to the leavepiece as a whole the Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled. It did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that since the Panel considered that its rulings at Point B1 applied here in relation to page 4 of the leavepiece, it repeated its position set out in B1. Novo Nordisk noted that as it had accepted other rulings, these leavepieces would be withdrawn.

COMMENTS FROM LILLY

There were no comments from Lilly.

APPEAL BOARD RULING

The Appeal Board noted its comments and rulings in Point B1 above regarding the advertisement which it considered also applied to page 4 of the leavepiece at issue.

5 Leavepiece 'Dosing: use one device, once a day' (UK/LR/0409/0077)

Page 1 of the leavepiece featured the picture of the lollipop tree and was headed 'Dosing: use one device, once a day' followed by 'Victoza allows convenient once-daily dosing at any time, independent of meals'.

Page 2 included a section headed 'Victoza can be used in combination with the following therapies'. This was followed by a chart which stated that 'no dose adjustments needed' for metformin or metformin plus thiazolidinedione.

COMPLAINT

Lilly alleged that the lollipop tree was misleading and inconsistent with the Victoza SPC and its licensed indication. Whilst the depiction of type 2 diabetes by analogy to a 'lollipop tree' was not unreasonable, the visual showed this tree being entirely uprooted. This implied that Victoza could uproot type 2 diabetes and eliminate it completely; Victoza would not cure diabetes as implied by the visual. Notwithstanding the latter, the visual also implied that Victoza delayed the progression of type 2 diabetes for which liraglutide was not licensed.

Lilly alleged that the heading 'Dosing: use one device, once a day' was ambiguous and misleading. Without reference to any other qualifying information on this page, the claim implied that Victoza could be used as monotherapy.

The claim that 'Victoza allows convenient once-daily dosing at any time, independent of meals' was ambiguous and inconsistent with Section 4.2 of the SPC which stated that '… it is preferable that Victoza is injected around the same time of day, when the most convenient time of day has been chosen'. This would suggest some regulatory and pharmacokinetic related restrictions and considerations around the need to establish and maintain the timing of injections; this was clearly at odds with the claim, which suggested that, day to day, patients could freely alter the time of their injection. The claim also appeared on page 3 of the leavepiece.

The statement on page 2 that 'No dose adjustments needed' with respect to metformin and metformin and thiazolidinedione when combined with Victoza was misleading and incorrect as it suggested that dose adjustments would never arise with respect to any component of these combinations; this was not consistent with the real-life clinical situation and the Victoza SPC.

For the reasons outlined above Lilly alleged that this leavepiece was in breach of Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.8, 7.10, 8.1 and 9.1 of the Code.

RESPONSE

Novo Nordisk referred to its response in Point B1 regarding the visual. There was no intended suggestion of uprooting, eliminating or otherwise curing diabetes. The advertisement specifically summarised the impact of Victoza on physiological abnormalities seen in type 2 diabetes and called for physicians to consider more than blood glucose in their treatment.

Novo Nordisk did not agree that the headline 'Dosing: use one device, once a day' referred to anything other than the dosing and delivery of Victoza. Given that the claim did not refer to any concomitant treatment (all of which were oral treatments in any event), Novo Nordisk refuted that the claim implied that Victoza could be used as monotherapy.

The claim 'Victoza allows convenient once-daily dosing at any time, independent of meals' was not ambiguous and was consistent with the SPC which stated: 'Victoza is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site and timing can be changed without dose adjustment'. The comment in the SPC that 'However, it is preferable that Victoza is injected around the same time of the day, when the most convenient time of the day has been chosen' would refer to any medicine – no physician would recommend that a patient actively varied the time of administration of a medicine on a day-to-day basis since, at the very least, this could lead to missed doses and reduced adherence. However, there were no regulatory or pharmacokinetic related restrictions and considerations around the need to establish and maintain the timing of injections.

Novo Nordisk was confused by Lilly's allegation that the statement that 'No dose adjustments needed with respect to metformin and metformin + thiazolidinedione when combined with Victoza was inconsistent with the SPC. The SPC stated that 'Victoza can be added to existing metformin or to a combination of metformin and thiazolidinedione therapy. The current dose of metformin and thiazolidinedione can be continued unchanged'.

PANEL RULING

The Panel noted its rulings regarding the lollipop tree in Point B1 above which it considered applied here.

With regard to the claim 'Dosing: use one device, once a day' the Panel considered that the front page of the leavepiece was not sufficiently clear that Victoza was to be used in combination with oral antidiabetic agents rather than as monotherapy. The claim was misleading. A breach of Clause 7.2 was ruled. This ruling was appealed.

The Panel considered the claim 'Victoza allows convenient once-daily dosing at any time independent of meals' was ambiguous and misleading given the specific mention in the SPC that '… it is preferable that Victoza is injected around the same time of day, when the most convenient time of day has been chosen'. A breach of Clause 7.2 was ruled. This ruling was appealed.

With regard to page 2, the Panel noted that it was stated that when Victoza was administered with metformin or with metformin plus a thiazolidinedione, no dose adjustments were needed. The SPC stated that Victoza could be added to existing metformin or to a combination of metformin and thiazolidinedione therapy. The current dose of metformin and thiazolidinedione could be continued unchanged. The Panel thus did not consider that the statement in the leavepiece was misleading or incorrect as alleged. No breach of Clause 7.2 was ruled.

During its consideration of this matter the Panel was concerned that the statement 'Victoza can be used in combination with the following therapies' might be read as implying that combination therapy was optional and that Victoza could be used as monotherapy. The word 'can' implied a choice in that regard the Panel asked that Novo Nordisk be advised of its concerns.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. This ruling was appealed. The Panel was concerned that the leavepiece was not

clear about the indications for a new product and implied that it could be used as monotherapy. The Panel decided on balance that the leavepiece brought discredit upon the industry and a breach of Clause 2 was ruled. This ruling was appealed.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that whilst it might not have been instantly obvious from the front page, that Victoza was to be used in combination with oral antibiotic agents rather than as a monotherapy page 2 of the leavepiece focused on the licensed indication and the potential combinations in which Victoza could be used according to its licence. Novo Nordisk did not believe that health professionals would only read the front page of a leavepiece which contained information about dosing of a medicine, and thus the leavepiece should be considered as a whole. It was reasonable to expect that health professionals would read the information contained in the material before interpreting it and on that basis the leavepiece was not misleading.

Novo Nordisk noted that whilst it knew that Clauses 7.2 and 7.4 of the Code and Regulation 3A(2) and (3) of the Advertising Regulation and Paragraph 4.3 of the Blue Guide were not entirely equivalent, pre-vetting against such requirements took place. Novo Nordisk therefore did not agree with the Panel that the leavepiece was misleading and in breach of Clause 7.2.

Novo Nordisk disagreed with the Panel that 'Victoza allows convenient once-daily dosing at any time independent of meals' was ambiguous and misleading in light of the statement in the SPC that it was preferable for Victoza to be injected at the same time of day. The SPC stated that it was preferable to inject Victoza at the same time of the day, not that this was a requirement. The SPC required that Victoza was injected once a day. The SPC also indicated that it could be injected anytime of the day independent of meals. This requirement and the highlighted competitive advantage of Victoza vs exenatide (ie independent of meals) were reflected in the materials.

Novo Nordisk reiterated its comments above about pre-vetting and thus appealed the ruling of breach of Clause 7.2.

Novo Nordisk did not understand the rulings of a breach of Clause 9.1 and, particularly, the breach of Clause 2 in this case. Novo Nordisk submitted that even if it accepted the ruling relating to the front page, and leaving aside the fact that the MHRA had pre-vetted the materials, the item contained a clear indication how to use Victoza on page 2. Undoubtedly there was no intention to deliberately mislead the audience. Furthermore the lack of information about the preferred time of injection could not be considered as compromising patient safety. Using Victoza at the same time each day was a preference, not a necessity. Novo Nordisk noted that the US new drug application for Victoza did not require that the product carry this recommendation which might perhaps put it in some context.

On the basis of the above Novo Nordisk strongly disagreed with the Panel that this material was in breach of Clauses 9.1 and 2 of the Code.

COMMENTS FROM LILLY

Lilly alleged that Novo Nordisk's assertion that the claim 'Victoza allows convenient once-daily dosing at any time independent of meals' was inconsistent with the SPC and ambiguous. This unqualified claim was misleading and ignored the very specific instruction in the SPC regarding the need for patients to establish and adhere to the most convenient time of day for injecting liraglutide. Arguably, if this was not deemed to be an important aspect for safe use it was likely that its inclusion in the product label would not have been considered necessary by the licensing authorities.

APPEAL BOARD RULING

The Appeal Board considered that the claim 'Dosing: use one device, once a day', on the front page of the leavepiece, was not sufficiently clear that Victoza was to be used in combination with oral antidiabetic agents rather than as a monotherapy. In addition page 2 of the leavepiece stated that 'Victoza **can be** used in combination with the following therapies' (emphasis added) which implied an element of choice in the matter and reinforced the impression that Victoza could be used as a monotherapy. The Appeal Board considered that the claim at issue on the front page of the leavepiece was misleading and thus upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

The Appeal Board considered that despite the statement in the SPC that '…it is preferable that Victoza is injected around the same time of day when the most convenient time of day has been chosen' the claim 'Victoza allows once-daily dosing at any time independent of meals' was not ambiguous or misleading. Victoza was a once daily medicine and in that regard prescribers would expect there to be an approximate 24 hour gap between doses. The Appeal Board ruled no breach of Clause 7.2. The appeal on this point was successful.

The Appeal Board considered that although the leavepiece had been ruled in breach of Clause 7.2 it did not consider that there had been a failure to maintain high standards or that discredit had been brought upon the industry. The Appeal Board ruled no breach of Clauses 9.1 and 2. The appeal on these points was successful.

C Patient Support Materials

1 Booklet 'Victoza Guide – Making a fresh start with Victoza' (UK/LIRA/0609/018)

The front cover of the booklet included the

company name and logo as well as in the bottom right corner the claim 'New' followed by the product logo (brand name and generic name).

COMPLAINT

Lilly had a number of concerns regarding this booklet. The design, style and content was closely associated with that of the promotional materials discussed in point B above; this was therefore promotion of Victoza to patients. This was evidenced by the significant reliance on the liraglutide branding colours, inclusion of promotional messages and brand name throughout this booklet. For example, starting from the front cover, which referred to 'Victoza' three times, the booklet referred to the brand name no less than eighty-nine times! This went well beyond the legitimate purpose of product identification. To compound matters, injection needles manufactured by Novo Nordisk, NovoFine and NovoTwist, were also referred to by brand name.

The reference to new Victoza on the cover page was a promotional claim that was not relevant or appropriate for patients who had already been prescribed the medicine.

The last paragraph on page 5 informed patients that the risk of hypoglycaemia with Victoza was minimised due to its mode of action. This was not only inappropriate and irresponsible but clearly promoted Victoza to patients with regard to its safety. Lilly noted that having referred to hypoglycaemia, the booklet failed to inform or provide any guidance of how to manage the common occurrence of this important adverse event which might arise particularly when Victoza was combined with a sulphonylurea; this omission was clearly deliberate in order to minimise or understate the occurrence of hypoglycaemia with Victoza.

Page 8 of the booklet, informed about the posology and method of administration of Victoza and the timing requirements for the injection. The style and wording used was the same as that in the leavepiece UK/LR/0409/0077 (point B5 above); this showed that Novo Nordisk had employed this patient information booklet to promote Victoza.

Similarly, on page 18 of the booklet the promotional claim '… fit Victoza into your life better' was presented in an emboldened font. This showed that the Victoza patient support materials were being used as an advertising platform.

For the reasons outlined above Lilly alleged that the Victoza patient support materials were in breach of Clauses 2, 9.1, 12.1, 22.1, 22.2 and 22.5.

Lilly also believed that these patient support materials breached the MHRA Blue Guide on the Advertising and Promotion of Medicines in the UK, which prohibited the promotion of prescription only medicines to patients and the public.

RESPONSE

Novo Nordisk submitted that the booklet was designed and developed for patients who had been prescribed Victoza as support material to help with different aspects of their new treatment. As such, it could not be considered a promotional item.

Novo Nordisk disagreed that this material should have a detailed discussion on how to handle hypoglycaemic events. The booklet did not replace consultation with a health professional, thus the area of concern on how to deal with such an event should be covered in detail with the health professional. Furthermore the section about side effects clearly referred patients to the patient information leaflet which dealt with this issue.

PANEL RULING

The Panel did not consider that the fact that the design, style and content of material for patients was closely associated with the various promotional materials meant that the patient material was therefore unacceptable. What was important was whether such material met the requirements of Clause 22.

It was not unacceptable for patients prescribed a product to be given information about that product provided, as stated in the supplementary information to Clause 22.2, that such information was factual and non-promotional. The Panel was concerned that the front page of the patient booklet included the product logo plus the claim 'New'. This implied that the content was promotional. This impression was compounded by the positive statement 'Making a fresh start with Victoza'. Such promotional branding combined with a claim should not be used in patient materials. In the Panel's view the front page was, in effect, an advertisement for a prescription only medicine and a breach of Clause 22.1 of the Code was ruled. This ruling was appealed.

The Panel did not consider that it was unacceptable to refer to NovoFine and NovoTwist needles in relation to the section 'Prepare your pen'. Lilly had not given details as to where in the booklet references appeared. No breach of Clauses 22.1 and 22.2 was ruled.

Page 5 referred to 'The science bit' and stated that, because of the way Victoza worked, the risk of hypoglycaemia was minimised. Advice on how to cope with hypoglycaemia would have been helpful but as patients prescribed Victoza would have already been prescribed other medicines which could possibly cause hypoglycaemia, in that regard they should already know what to do. The Panel noted however that the Victoza SPC listed hypoglycaemia as a common event (in combination with both metformin and glimepiride) or a common event (in combination with either metformin and rosiglitazone or in combination with glimepiride alone). Clause 22.2 of the Code required that patient

material must not be misleading about the safety of a product. Given the statement in the Victoza SPC about hypoglycaemia, the Panel did not consider that to state that the risk of hypoglycaemia was minimised with Victoza was fair or balanced; it misled with regard to the safety of the product. A breach of Clause 22.2 was thus ruled.

Page 8 was headed 'Step-by-step injection guide' and stated 'You should inject Victoza only once a day, at any time of day, with or without eating food first. But it's best if you use Victoza at the same time every day – so pick a time you won't forget'. The Panel did not consider that this page of the booklet promoted Victoza to the public as alleged. That the style and wording bore similarities to the promotional item considered at point B5 above was not, in itself, unacceptable. The information was in line with the SPC unlike that in point B5 above. No breach of Clauses 22.1 and 22.2 were ruled.

The Panel did not consider that the statement on page 18 'Here are a few tips to help you fit Victoza into your life better' was a promotional claim. This section referred to the need to take medicine regularly in order to get the full benefits and referred readers to sources of help. The Panel did not consider that the page advertised Victoza to the public. Readers would have been prescribed the product. The information was not unreasonable. The Panel ruled no breach of Clauses 22.1 and 22.2.

The Panel noted its ruling of a breach of Clause 22.1 in relation to the front page. However, the Panel did not consider that overall the booklet was promotional material that had been disguised as information to patients. No breach of Clause 12.1 was ruled.

During its consideration of this point the Panel was concerned about the impression given by the front page about the origin of the material. 'freshstart Diabetes support from people like you' appeared prominently in the top left hand corner in the same font colour as the Victoza logo. In addition to the Victoza logo the brand name appeared twice below the freshstart logo. The only reference to Novo Nordisk was beneath the company logo which was blue and appeared in a very small font in the lower left hand corner. Patients might assume that the leaflet came from Freshstart which, from its description on the front page, appeared to be a patient organisation. The role of the company in producing the booklet or running the FreshStart Programme was not sufficiently clear. There was no allegation before the Panel on this point. The Panel requested that Novo Nordisk be advised of its concerns.

The Panel ruled no breach of Clause 22.5 which required that companies were responsible for information about products issued by their public relations agency. This was a statement of principle, it was not a requirement of the Code that could be breached.

With regard to Lilly's comments about the MHRA Blue Guide the Panel noted that it could only consider the allegations in relation to the Code and not the MHRA Blue Guide or UK law.

The Panel considered that the use of the Victoza logo and the claim 'new' meant that high standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel did not consider that on balance the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

APPEAL BY NOVO NORDISK

Novo Nordisk noted that as it had accepted the ruling of the breach of Clause 22.2, it had withdrawn this booklet.

Novo Nordisk disagreed with the Panel that using a single product logo on material which was disseminated only to Victoza patients would make a 22 page booklet promotional. Novo Nordisk further noted that although the Panel noted its ruling of a breach of Clause 22.1 in relation to the front page, overall the Panel did not consider that the booklet was promotional material that had been disguised as information to patients.

Novo Nordisk submitted that as only existing users of Victoza would see the booklet and that the product packaging carried the Victoza logo, it did not understand how using the logo on the booklet made it promotional.

Novo Nordisk noted that the prohibition on use of the word 'new' in Clause 7.11 of the Code was limited to where a product had been generally promoted for more than 12 months in the UK. There did not seem to be any other relevant Code provision. Therefore it did not understand the Panel's objection to the use of the word, since Victoza had not been generally promoted for more than 12 months in the UK.

Novo Nordisk did not agree with the Panel that the patient booklet was in breach of Clause 22.1 of the Code.

COMMENTS FROM LILLY

There were no comments from Lilly.

APPEAL BOARD RULING

The Appeal Board considered that the use of the Victoza logo in combination with the claim 'New' promoted Victoza. This was compounded by the positive statement 'Making a fresh start with Victoza'. Such promotional branding combined with a claim should not be used in patient material. It was irrelevant that patients would know the brand name. In the Appeal Board's view the front page, was, in effect, an advertisement to the public for a prescription only medicine and it upheld the Panel's ruling of a breach of Clause 22.1 of the Code. The

appeal on this point was unsuccessful.

2 Website 'www.MyDiabetesFreshStart.co.uk' (UK/LIRA/0509/001, 002, 003, 004, 005, 007)

COMPLAINT

Lilly stated that it had a number of concerns regarding this website.

As discussed in point C1 above, the design, style and content of the website was such as to promote and advertise Victoza to patients. This was evidenced by the significant reliance on the product branding, promotional messages and numerous mentions of 'Victoza' throughout eg the webpage entitled 'Victoza FAQs' [frequently asked questions] referred to 'Victoza' twenty-three times; additionally 'Victoza' was used twenty-two times within the responses to the FAQs.

The points discussed above with regard to the booklet (point C1) were also pertinent to the webpage entitled 'About Victoza'.

For the reasons outlined above Lilly alleged that the website was in breach of Clauses 2, 9.1, 12.1 22.1, 22.2 and 22.5 of the Code.

Lilly also believed that the website breached the MHRA Blue Guide on the Advertising and Promotion of Medicines in the UK, which prohibited the promotion of prescription only medicines to patients and the public.

RESPONSE

Novo Nordisk stated that the website was developed as a post prescription site for patients already prescribed Victoza (access to the site was granted by using the barcode on the packaging), therefore the site was not promotional.

Novo Nordisk denied that the website was in breach of the clauses as alleged.

PANEL RULING

The Panel noted that its comments regarding the alleged breach of the MHRA Blue Guide in point C1 above also applied here.

The Panel did not accept Novo Nordisk's submission that as the site was developed for patients as a post prescription site it was not promotional. Whether the site was promotional depended, *inter alia*, on its content. Whilst patients for whom the prescribing decision had been made could be provided with information about their medicine, such information must not be promotional.

The Panel noted the comments it had made about the booklet at issue in point C1 above. The Panel noted that many of the webpages included the brand logo. The Panel considered that this was unacceptable and constituted the promotion of a prescription only medicine to the public. A breach of Clause 22.1 was ruled. This ruling was appealed. The Panel considered that in this regard high standards had not been maintained and a breach of Clause 9.1 was ruled. This ruling was appealed. However, the Panel did not consider that overall the booklet was promotional material that had been disguised as information to patients. No breach of Clause 12.1 was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

The Panel noted that Lilly had not provided detailed allegations about the webpage entitled 'About Victoza' it had relied on its allegations in point C1 above. It was not for the Panel to identify Lilly's allegations based on this cross reference approach. Insufficient detail had been provided thus the Panel decided not to rule on this general allegation. If Novo Nordisk accepted the Panel's rulings regarding point C1 it would have to check the website to ensure that any similar material was withdrawn as would be required by signing the requisite form of undertaking.

The Panel ruled no breach of Clause 22.5 which required that companies were responsible for information about products issued by their public relations agency. This was a statement of principle, it was not a requirement of the Code that could be breached.

APPEAL BY NOVO NORDISK

Novo Nordisk disagreed with the Panel's rulings and noted that the Panel stated that whether a website was promotional depended, *inter alia*, on its content and did not consider the overall material was promotional. Where the overall material was not promotional, it was hard to see how using the product logo on a webpage which was dedicated to Victoza-users made the webpage promotional. Furthermore, as mentioned in C1 above, the Victoza logo was on the product packaging. This could only be accessed by patients already using the product and Novo Nordisk reiterated the point made in C1 in this regard.

Novo Nordisk further submitted that it was inappropriate and unjust for the Panel to rule a breach of Clause 22.1 of the Code when the same item was approved by the MHRA as being in compliance with paragraph 5.2 of the Blue Guide.

Novo Nordisk therefore did not agree with the Panel that the website was in breach of either of Clauses 22.1 or 9.1 of the Code.

COMMENTS FROM LILLY

There were no comments from Lilly.

APPEAL BOARD RULING

The Appeal Board noted the comments it had made

about the booklet at issue at Point C1 above. Unlike the booklet the web pages now at issue did not include the claim 'New'. 'Fresh start' appeared as the name of the patient programme, which in the Appeal Board's view did not have the same effect as a claim 'Making a fresh start with Victoza' which was used in the booklet at issue in Point C1. The Appeal Board was concerned that the brand name was used frequently. However it did not consider that the web pages constituted the promotion of a prescription only medicine to the general public. The Appeal Board ruled no breach of Clause 22.1 and in that regard considered that Novo Nordisk had not failed to maintain high standards. The Appeal Board ruled no breach of Clause 9.1. The appeal on both points was successful.

D Liraglutide Formulary Pack

In response to these allegations Novo Nordisk had provided the Liraglutide Formulary Pack (UK/LR/0609/0218) dated July 2009. This consisted of four sections and appeared to include a set of slides and was considered by the Panel as follows.

1 Section 1 - 'The burden of type 2 diabetes'

COMPLAINT

Section 1.1, 'Executive summary', consisted of a number of bullet points which included the following:

> 'There are a number of unmet challenges in the management of T2D [type 2 diabetes], including inadequate glycaemic control, blood pressure control and treatment adherence.
>
> In addition, many currently available therapies are associated with significant limitations, such as hypoglycaemia and weight gain.
>
> There is therefore a need for novel treatments that address current unmet needs.
>
> Novo Nordisk is a world leader in the development of treatments for diabetes ....'.

Lilly alleged that these statements, in support of the promotion of Victoza, were misleading, could not be substantiated, exaggerated the facts and invited a comparison of Victoza with other antidiabetic agents with respect to efficacy and safety. Novo Nordisk asserted that compared with other, undefined, antidiabetic agents its novel treatment Victoza addressed an unmet need with respect to achieving adequate glycaemic control, no weight gain, improved treatment adherence and an improved side-effect profile with particular regard to the incidence of hypoglycaemia; this claim was disparaging, could not be substantiated and exaggerated the facts with respect to treatments such as Byetta. Further, the claims implied that Victoza also fulfilled an unmet need with respect to reductions in blood pressure and weight, for which it was not licensed.

The above assertions were also evidenced by the content of Section 1.6, 'Unmet challenges in T2D treatment', which included statements such as 'Despite advances in the management of T2D, current treatment options have important deficiencies. These include hypoglycaemia as a potential adverse event, and a high risk of weight gain'. This sweeping generalisation invited a misleading comparison of Victoza with different classes of antidiabetic agents some of which might be the only option for individual patients eg those who required insulin due to beta-cell failure. The section then went on to discuss various 'unmet challenges' with particular reference to 'Beta-cell decline and glucose control', 'BMI and weight', 'Hypoglycaemia', 'Blood pressure' and 'Treatment adherence'. Given the context of the discussion regarding unmet needs, Lilly was surprised that the reader was not also informed about the availability of Byetta which was the first-in-class GLP-1 receptor agonist and which addressed all of the unmet challenges referred to in this section; this misled the reader by omission. The statement in Section 1.6.4, 'Blood pressure', that 'Most treatments for T2D do not affect systolic blood pressure' further demonstrated Novo Nordisk's intention to discuss Victoza as an anti-hypertensive treatment; an unlicensed indication.

In Section 1.7, 'Novo Nordisk: A world leader in diabetes care', the statement that Victoza was '... the first once-daily human glucagon-like peptide-1 (GLP-1) analogue developed for the treatment of T2D' misled the reader by omission. In the absence any mention of Byetta the impression created was that liraglutide was the first licensed product in this particular class.

Section 1.8, 'Conclusion', reinforced the statements, discussed above which were misleading, not capable of substantiation, exaggerated the facts and disparaged other antidiabetic agents, and in particular Byetta, with respect to their efficacy and safety as compared to liraglutide.

For the reasons outlined above Lilly alleged that sections were in breach of Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.8, 7.9, 7.10, 8.1, 9.1 and 10.2 of the Code.

RESPONSE

Novo Nordisk stated that the statements at issue were general statements in the introduction to the pack which set the scene regarding the unmet challenges with regard to the treatment of type 2 diabetes and had been taken out of context. There were no claims in this section that Victoza, or any other treatment could eliminate these challenges. There were no comparisons direct or indirect between Victoza and other antihyperglycaemic agents in this section. Thus Novo Nordisk did not agree with Lilly's allegation that the statements in context with Victoza were misleading and not capable of substantiation.

Section 1.6: Novo Nordisk noted Lilly's statement that Byetta addressed all of the unmet challenges described in the section. Novo Nordisk believed that GLP-1 analogues as a class might address the unmet challenges although to different extents. The intended context of this introductory section was to set the scene as to the challenges with regard to the treatment of type 2 diabetes, rather than to detail the extent to which each GLP-1 analogue could address these challenges. As such, it was intentional that no particular products were mentioned in this general introductory section.

Liraglutide was only mentioned in the last paragraph of Section 1.7, 'Novo Nordisk: A world leader in diabetes care', and not in relation to any promotional or therapeutic claim. Section 2.5 'The Lead Programme', was dedicated to the randomized clinical trials with liraglutide and provided details about the randomised controlled trial comparison of Victoza and Byetta (Buse *et al* 2009 (LEAD 6)). Therefore providing a balanced view within the pack. Novo Nordisk believed it was reasonable to suppose that the target audience (budget holders) read the whole document and received the relevant information about both products and their comparison and not just Section 1 in order to obtain information regarding type 2 diabetes.

Section 1.7: Novo Nordisk disagreed with Lilly that the statement 'liraglutide, the first once-daily human glucagon-like peptide-1 (GLP-1) analogue developed for the treatment of T2D' was misleading. Liraglutide was the first once-daily human glucagon-like peptide analogue developed for the treatment of type 2 diabetes.

Section 1.8: This section provided a short conclusion and provided a general summary of the challenges with the treatment of type 2 diabetes; as such Novo Nordisk referred to its comments with regard to Sections 1.1, and 1.6 above.

PANEL RULING

The Panel considered that Sections 1.1 to 1.6 constituted a general discussion on the burden of type 2 diabetes. General comments were made about what was described as 'important deficiencies' of currently available therapies. Nonetheless, these sections were an integral part of the formulary pack; the Victoza logo with the word 'new' appeared on the front cover of the section. There was thus, at the very least, an expectation in the mind of the reader that Victoza as a 'new' medicine would not have the deficiencies associated with current therapy. Such an expectation was compounded by statements such as 'prevention of weight gain **must** be a target for treatment alongside glycaemic control.' (emphasis added), (Section 1.6.2). The Panel considered that the purpose of Section 1 overall was, *inter alia*, to establish a need for those additional benefits which might be provided by Victoza and to state where current therapies failed. The challenge of BMI and weight was given equal emphasis to glycaemic control. The Panel considered that the section implied that Victoza would positively address all of the unmet challenges. The Panel noted its comments and rulings above on Victoza's effect on secondary benefits. Breaches of Clauses 3.2, 7.2, 7.3, 7.4 and 7.10 were ruled.

The Panel considered that the description of the unmet challenges in type 2 diabetes treatment in Section 1.6 'Unmet challenges' and Section 1.8 'Conclusion' could also be interpreted as implying that no product currently available met any one of these challenges. The Panel considered that this was misleading as the challenges and the differences between current treatments were not defined in detail. The Panel considered that this section was too general and thus misleading, it disparaged current treatments and the impression given was not capable of substantiation. A breach of Clauses 7.2, 7.3, 7.9, 7.10 and 8.1 was ruled in relation to Section 1.6 and Section 1.8.

The Panel noted that Victoza was described as 'the first once-daily human glucagon-like peptide-1 (GLP-1) analogue developed for the treatment of T2D' in Section 1.7. The Panel noted, however, that although Victoza was the first **once daily** human GLP-1 analogue it was in fact the second GLP-1 analogue to be marketed. In that regard the Panel considered that the statement was ambiguous and thus misleading. It was unclear as to which part of the statement 'first' applied to. A breach of Clause 7.2 was ruled. This ruling was appealed.

The Panel noted that Lilly had alleged a breach of Clauses 7.8 and 10.2 of the Code without giving any details of what was the subject of the allegations. In the circumstances the Panel considered that insufficient detail had been provided by Lilly and thus no breach of Clauses 7.8 and 10.2 were ruled.

The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

APPEAL BY NOVO NORDISK

Novo Nordisk accepted the ruling of a breach of Clause 3.2, but on the basis that there was no objection in principle to the provision of background information about the company in promotional material. The formulary pack had been withdrawn.

Novo Nordisk submitted that the proximity of the adjective 'first' to the wording of 'once-daily' in the claim that Victoza was 'the first once-daily human glucagon-like peptide-1 (GLP-1) analogue' inevitably led to the interpretation that this was what the adjective related to. Liraglutide was the first GLP-1 analogue which could be injected once-daily, since exenatide should be injected twice, and the

statement was not misleading.

It was inappropriate and unjust that the Panel ruled a breach of Clause 7.2 of the Code as the item was approved by the MHRA as being in compliance with Regulation 3A(2) and (3) of the Advertising Regulation and Paragraph 4.3 of the Blue Guide.

Therefore Novo Nordisk did not agree with the ruling by the Panel that the claim was in breach of Clause 7.2 of the Code.

APPEAL BOARD RULING

The Appeal Board noted that Victoza was described as 'the first once-daily human glucagon-like peptide-1 (GLP-1) analogue developed for the treatment of T2D' in Section 1.7 of the formulary pack. The Appeal Board considered that Victoza was the first **once daily** human GLP-1 analogue. The statement was not ambiguous or misleading, as 'first' immediately preceded 'once daily' it clearly referred to that. The Appeal Board ruled no breach of Clause 7.2. The appeal on this point was successful.

2 Section 2 - 'Clinical overview of liraglutide'

COMPLAINT

Section 2.1, 'Executive Summary' included the statement that liraglutide was '… the first once-daily human glucagon-like peptide (GLP)-1 analogue …' and Lilly alleged that this misled the reader by omission. In the absence of any mention of Byetta the impression created was that liraglutide was the first licensed product in this particular class.

The claim that 'Liraglutide is administered once daily and can be given at any time of day, independently of meals …' was alleged to be ambiguous and inconsistent with Section 4.2 of the Victoza SPC as outlined above in point B5.

Again, the weight reduction and blood pressure reduction benefit associated with Victoza were discussed as though this were a licensed indication and not a secondary/additional benefit of the treatment after achieving glycaemic control. The misleading aspect of the latter was as discussed above in points B3 and B4. Lilly referred to Section 2.1 and Sections 2.5.2, 'Liraglutide and body weight', and 2.5.3, 'Liraglutide and SBP', stating that the latter was one of the boldest examples of inviting consideration of Victoza as a licensed treatment for systolic hypertension.

Section 2.3, 'Pharmacology and pharmacokinetics', discussed the importance of Victoza and beta-cell function and stated that 'Beta-cell function is important in the progression of T2D; many current therapies do not address this issue'. This unqualified statement invited a comparison with all antidiabetic agents and asserted that only Victoza improved beta-cell function, unlike agents such as Byetta, and positively impacted the progression of type 2 diabetes. There was no clinical evidence that Victoza delayed or halted the progression of type 2 diabetes. This disparaging claim could not be substantiated, and exaggerated the facts. In this particular regard, the statement that 'Data from animal studies demonstrated a significant increase in beta-cell mass after 6 weeks of liraglutide compared with controls' proposed a putative mechanism by which Victoza effected the implied delay or halt in disease progression in patients with type 2 diabetes. This assertion was misleading and could not be substantiated and implied that Victoza changed non-functional beta-cells into cells which could produce insulin. This claim also relied on extrapolating and exaggerating the clinical significance and relevance of data derived from animal studies to patients.

Section 2.4.4, 'Method of administration' invited a comparison with Byetta with respect to posology and method of administration. Lilly stated that as per its comments above about Section 2.1, the statement 'In contrast to twice-daily exenatide, liraglutide can be administered once daily, independent of mealtimes and can be taken at any time of the day' was misleading and inconsistent with the Victoza SPC.

Sections 2.5.5, 'Safety and tolerability', 2.5.5.1 'Hypoglycaemia', and 2.5.5.2 'Adverse events', discussed the incidence and severity of hypoglycaemia with reference to results from Buse *et al* (LEAD 6). Lilly's concerns outlined with regard to Section 2.5 were applicable here. Lilly noted that the discussion of the comparative incidence of nausea in Buse *et al* (LEAD 6) was reported as being similar for Victoza and Byetta but the reader was additionally told that the '… nausea persisted longer with exenatide than with liraglutide' which was unbalanced and misleadingly implied that no liraglutide subjects experienced nausea at the 26 week study end time-point.

In Section 2.6, 'Conclusion', the statements that '… liraglutide could be particularly useful if weight gain is a concern' and 'As majority of patients with T2D have hypertension, the reduction of SBP with liraglutide should be beneficial to most patients' clearly misled readers to consider Victoza as a licensed treatment for systolic hypertension and obesity. Indeed, to compound matters, Section 2.7, 'Frequently asked questions', offered a putative mechanism by which Victoza might reduce blood pressure.

For the reasons outlined above Lilly alleged that these sections were in breach of Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.8, 7.9, 7.10, 8.1, 9.1 and 10.2.

RESPONSE

Novo Nordisk submitted that the statement 'the first once-daily human glucagon-like peptide (GLP) - analogue' in Section 2.1 was not misleading and was capable of substantiation as evidenced by the

difference between the Victoza and Byetta SPCs. Novo Nordisk also believed the claim regarding the administration of Victoza reflected the SPC, which stated at Section 4.2 that it could be administered 'at any time'. Novo Nordisk referred to its comments in point B5 above.

With regard to the allegation about information on weight reduction, Novo Nordisk referred to its response in relation to points B3 and B4 above.

In addition Novo Nordisk stated that the discussion of the effect of liraglutide on weight and systolic blood pressure in Section 2.3 was derived from pre-specified endpoints of six large, randomised, controlled clinical trials (Marre *et al* 2009 (LEAD 1), Nauck *et al* 2009 (LEAD 2), Garber *et al* 2008 (LEAD 3), Zinman *et al* 2009 (LEAD 4), Russell-Jones *et al* 2009 (LEAD 5) and Buse *et al* 2009 (LEAD 6)), all of which had been published in peer reviewed journals. Using this data as evidence of liraglutide's full therapeutic effect was entirely appropriate and provided clinicians and budget holders with relevant information to help them make a rational assessment of Victoza's characteristics. There was no claim or inference that weight management or blood pressure control were licensed indications.

The statement 'Beta-cell function is important in the progression of T2D; many current therapies do not address this issue' was sufficiently qualified with regard to the nature of the findings, in terms of beta-cell mass (animal data, in vitro data, Sturis *et al* 2003). It was reasonable to point out that such findings might have clinical implications (delay/halt disease progression) as highlighted in the document. Further, it was true that other therapies did not address this issue.

Section 2.4.4: Novo Nordisk did not agree with Lilly that the statement 'In contrast to twice-daily exenatide, liraglutide can be administered once daily, independent of mealtimes and can be taken at any time of the day' was misleading and inconsistent with the liraglutide SPC. This statement simply reflected the differences between the Byetta and Victoza SPCs. Novo Nordisk also referred to its response in relation to Section 2.1 above.

Sections 2.5.5, 2.5.5.1, 2.5.5.2: With regard to Lilly's concern the fact that nausea in Buse *et al* (LEAD 6) persisted longer with Byetta than with Victoza, Novo Nordisk referred to Buse *et al* (LEAD 6) that 'although the incidence of nausea was similar initially, it was less persistent with liraglutide'. Therefore Novo Nordisk disagreed with the allegation regarding these sections and referred to its response in relation to Section 2.5 above.

Section 2.6: With regard to Lilly's concerns that the statements 'liraglutide could be particularly useful if weight gain is a concern' and 'As majority of patients with T2D have hypertension, the reduction of systolic blood pressure with liraglutide should be beneficial to most patients' were misleading and led readers to believe liraglutide was a licensed treatment for systolic hypertension and obesity, Novo Nordisk submitted that the statements had been taken out of context. Section 2.6 was a conclusion section, which started by noting the glycaemic efficacy and only mentioned potential weight loss and a drop of systolic blood pressure as added benefits of Victoza, which 'could' and 'should', not 'will' benefit patients. It was also clear when Section 3 was read as a whole that these conclusions were in relation to the findings of the study rather than the licensed indication of Victoza.

PANEL RULING

The Panel considered that its ruling of a breach of Clause 7.2 in point D1 above regarding the claim 'first once-daily human glucagon-like peptide (GLP)-1 analogue' also applied here.

The Panel considered that in Section 2.1 the bullet point 'Liraglutide is administered once daily, and can be given at any time of day, independently of meals …' was similar to a claim at issue point B5 above in that the detailed advice in the SPC that '… it is preferable that Victoza is injected around the same time of day, when the most convenient time of day has been chosen' was not included. The Panel therefore ruled a breach of Clause 7.2 of the Code. This ruling was appealed.

The Panel noted that in Section 2.1 the second bullet point referred to Victoza's indication and the sixth bullet point referred to improvements in glycaemic control; this was immediately followed by another bullet point 'Significant weight loss in comparison with comparator drugs when liraglutide was used in combination treatment'. Section 2.4 'Indication and dosing' clearly set out the approved indication. The Panel noted that Section 2.5 'The LEAD Programme' ended with the sentence 'The clinical benefits of treatment with liraglutide observed with LEAD trials are reported here'. Sub-section 2.5.1 'Liraglutide and glycaemic control' was immediately followed by Section 2.5.2 'Liraglutide and body weight'. Sub-section 2.5.3 'Liraglutide and SBP' referred to reductions in blood pressure. The Panel considered that although the approved indication was given almost at the outset of Section 2 ie glycaemic control, additional benefits of therapy (effect on body weight and blood pressure) were given equal emphasis. They were not unequivocally distinguished from the main goal of therapy. In that regard the Panel did not consider that the secondary benefits were adequately placed within the context of Victoza licensed indication. A breach of Clause 3.2 was ruled. This ruling was appealed.

The Panel noted that the final paragraph of Section 2.3, 'Pharmacology and pharmacokinetics', discussed the data regarding the effect of Victoza on beta-cell function. It was stated that there was evidence to suggest that liraglutide improved and protected beta-cell function. It was further stated that beta-cell function was important in the progression of type 2 diabetes and that many

current therapies did not address this issue. In that regard the Panel did not consider that Section 2.3 implied that only Victoza improved beta-cell function as alleged. The fact that many current therapies did not address the issue implied that some did. In that regard the Panel did not consider that the statement was misleading or exaggerated; nor did it disparage other therapies. No breach of Clauses 7.2, 7.4, 7.10 and 8.1 were ruled.

The Panel was concerned, however, that the discussion about beta-cell function did not explain the clinical significance of the findings. Although Victoza had been shown to improve beta-cell function there was no data to show that this altered the clinical course of type 2 diabetes. Some readers might assume that the data meant that Victoza delayed or halted the progression of the disease. In this regard the Panel considered that the information given was misleading and that its clinical importance had been exaggerated. A breach of Clause 7.2 and 7.10 was ruled.

The Panel noted that Section 5.1 of the Byetta SPC stated that clinical studies with Byetta had indicated improved beta-cell function based on measures such as the homeostasis model assessment and the proinsulin to insulin ratio and that improved first and second phase insulin secretion after 52 weeks of Victoza was demonstrated in a subset of type 2 diabetics. The Panel did not consider that failure to specifically mention Byetta's effect on beta-cell function in Section 2.3 of the formulary pack was in itself misleading and no breach of Clause 7.2 was ruled.

With regard to Section 2.4.4 'Method of administration' the Panel considered that the comparison that 'In contrast to twice-daily exenatide, liraglutide can be administered once daily, independent of mealtimes and can be taken at any time of the day' was misleading. Although the information from the SPC that it was preferable that Victoza was injected around the same time of day when the most convenient time of day was chosen appeared later in the paragraph the Panel considered that it was misleading and inconsistent with the SPC to not state this immediately following the comparison with exenatide. A breach of Clauses 3.2, 7.2 and 7.3 was ruled. These rulings were appealed.

Section 2.5, 'The LEAD Programme', stated that Buse *et al* (LEAD 6) was the first study to provide a direct comparison between the two GLP-1 receptor agonists and that the study compared 1.8mg liraglutide added to metformin and/or glimepiride versus 10mcg exenatide. The Panel did not consider that Section 2.5 was misleading as alleged. The limited information about Buse *et al* (LEAD 6) did not claim differences between the products it merely listed this study as contributing to the clinical data. No breach of Clauses 7.2 and 7.3 was ruled.

The Panel noted that Section 2.5.5.1' 'Hypoglycaemia', went into more detail than Section 2.5 in relation to outcomes from Buse *et al* (LEAD 6). There was insufficient detail about the nature of Buse *et al* (LEAD 6) which the Panel considered should have been included – particularly with regard to the doses of Victoza and Byetta used and the fact that the study was open label. Insufficient detail had been provided and thus the claim regarding differences in hypoglycaemia was misleading. A breach of Clauses 7.2 and 7.3 was ruled. These rulings were appealed.

Section 2.5.5.2 'Adverse events' included details of the data for nausea from the LEAD studies. In Buse *et al* (LEAD 6) the difference in the proportion of patients with nausea at 26 weeks on liraglutide 1.8mg (3%) and exenatide (9%) was statistically significant $p<0.0001$. The Panel did not consider the claim that nausea persisted longer with exenatide than liraglutide implied that no patient experienced nausea at 26 weeks. A preceding sentence described it as one of the most frequently reported adverse events. No breach of Clauses 7.2 and 7.3 was ruled.

Section 2.6 'Conclusion' referred to reductions in HbA1c and the second paragraph commenced:

> 'The effective management of patients with T2D requires achievement of glycaemic control as well as reductions in cardiovascular risk factors. Treatment with liraglutide led to weight loss that was greatest in patients with a higher baseline BMI and occurred irrespective of nausea, suggesting that liraglutide could be particularly useful if weight gain is a concern. As the majority of patients with T2D have hypertension, the reduction of SBP with liraglutide should also be beneficial to most patients'.

The Panel noted the comments made previously about changes in weight. Section 2.6 implied that all patients would lose weight and this was not so. However the Panel did not consider that this section would mislead readers to consider liraglutide as a licensed treatment for hypertension and obesity as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that Lilly had alleged a breach of Clauses 7.8 and 10.2 of the Code without giving any details of what was the subject of the allegations. In the circumstances the Panel considered that insufficient detail had been provided by Lilly and thus no breach of Clauses 7.8 and 10.2 was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. This ruling was appealed. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that its appeal relating to

the ruling in D1 regarding the claim 'first once-daily human glucagon-like peptide (GLP)-1 analogue' also applied here. Novo Nordisk submitted that its appeal in Point B5 was relevant to its appeal of the breach of Clause 7.2 in relation to Section 2.1 and the time of injection of Victoza.

Novo Nordisk disagreed with the Panel that Section 2 was in breach of Clause 3.2 of the Code. This ruling had been made on the basis that, despite the approved indication being given almost at the outset of Section 2, the additional benefits were given equal emphasis. Novo Nordisk submitted that this was not so. As noted by the Panel, Section 2 started with the licensed indication of Victoza and two of the early subsections (2.1 and 2.4) clearly indicated the licensed indication; it was only later in Section 2 that the additional benefits were described.

Novo Nordisk noted that the Panel considered Section 2.4.4 was misleading and inconsistent with the SPC as it did not state the information from the SPC that it was preferable that Victoza was injected around the same time of the day immediately following the comparison with exenatide that, in contrast to exenatide, liraglitude could be administered once daily, independent of mealtimes and at any time of day. Novo Nordisk referred to its appeal in Point B5 which was relevant here to explain why it did not agree that the statement in the formulary pack was inconsistent with the SPC. Additionally, the information that it was preferable to inject Victoza at the same time each day was, in any event, provided later on in the same paragraph. Novo Nordisk submitted that the Panel's view that there was a breach simply because the information was later in the same paragraph, but not immediately after the statement, suggested that someone would ready only part of the paragraph; this seemed irrational. Novo Nordisk therefore disagreed with the Panel that Section 2.4.4 was in breach of Clauses 3.2, 7.2 and 7.3.

Novo Nordisk noted that the Panel considered that reporting of the hypoglycaemia results from LEAD 6 (Base *et al*) Section 2.5.5.1 was misleading due to the lack of information about the open-label nature of the trial, and the lack of clarification of the investigated Victoza and exenatide doses. Novo Nordisk noted that both compounds were used at their maximum recommended doses. The detection of the hypoglycaemic risk difference, was thus conducted using a fair, scientifically valid comparison. If the applied doses had not been comparable, the Panel's view would have been more relevant. Furthermore, Novo Nordisk failed to understand what impact the clarification of the open-label nature of the trial would have on the interpretation of the hypoglycaemic risk difference. More importantly Section 2.5 stated that a detailed description of the LEAD trials was provided at the end of Section 2, in the Appendix. For each LEAD programme, the main results were reported in Section 2.5 and detailed information about the design of each was provided in the Appendix.

Novo Nordisk did not agree with the Panel that Section 2.5.5.1 was misleading in breach of Clauses 7.2 and 7.3.

Novo Nordisk submitted that Section 2 complied with the spirit of the Code and did not breach any of the clauses ruled by the Panel. High standards had been maintained and Novo Nordisk therefore also disagreed with the Panel's ruling of a breach of Clause 9.1.

COMMENTS FROM LILLY

Lilly alleged that the claim that 'Victoza is the first once-daily human glucagon-like peptide (GLP)-1 analogue' was unclear and, intended to mislead the reader. The wording did not leave any opportunity for the reader, uninformed about Byetta, to consider anything but the assertion that Victoza was the first (GLP)-1 analogue to be licensed.

Whilst not materially relevant to this particular case, Lilly noted the serious breaches of Code in respect of Case AUTH/2234/5/09 and Case AUTH/2269/9/09 involving the promotion of liraglutide by Novo Nordisk. Lilly alleged this evidenced the continued and flagrant disregard by Novo Nordisk of both the spirit and tenet of the Code.

APPEAL BOARD RULING

The Appeal Board noted its comments and ruling of no breach of Clause 7.2 in Point D1 above regarding the claim 'first once-daily human glucagon-like peptide (GLP)-1 analogue' also applied here.

The Appeal Board considered that in Section 2.1 the bullet point 'Liraglutide is administered once daily, and can be given at any time of day, independently of meals …' was similar to the claim at issue Point B5 above. The Appeal Board considered that its comments and ruling of no breach of Clause 7.2 of the Code in Point B5 also applied here.

The Appeal Board noted that in Section 2.1 the second bullet point referred to Victoza's indication and the sixth bullet point referred to improvements in glycaemic control; this was immediately followed by the seventh bullet point 'Significant weight loss in comparison with comparator drugs when liraglutide was used in combination treatment'. Section 2.4 'Indication and dosing' repeated the indication. The Appeal Board noted that Sections 2.5.1 'Liraglutide and glycaemic control' was immediately followed by Section 2.5.2 'Liraglutide and body weight' and Section 2.5.3 'Liraglutide and SBP'. The Appeal Board considered that although the approved indication was given almost at the outset of Section 2 ie glycaemic control, additional benefits of therapy (effect on body weight and blood pressure) were given equal emphasis. They were not unequivocally distinguished from the main goal of therapy. In that regard the Appeal Board did not consider that the secondary benefits were adequately placed within the context of Victoza's licensed indication. The Appeal Board upheld the

Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful.

With regard to Section 2.4.4 'Method of administration' the Appeal Board considered that the comparison 'In contrast to twice-daily exenatide, liraglutide can be administered once daily, independent of mealtimes and can be taken at any time of the day' was not misleading. The information from the SPC that it was preferable that Victoza was injected around the same time of day when the most convenient time of day was chosen appeared later in the same paragraph. The Appeal Board ruled no breach of Clauses 3.2, 7.2 and 7.3. The appeal on this point was successful.

The Appeal Board noted that Section 2.5.5.1 'Hypoglycaemia', went into more detail than Section 2.5 in relation to outcomes from Buse *et al* (LEAD 6). The Appeal Board considered that it was not necessary to provide greater detail about Buse *et al* (LEAD 6). Both Victoza and Byetta were used at maximum dosage. In the context of the data the Appeal Board considered that the comparison regarding differences in hypoglycaemia was not misleading. The Appeal Board ruled no breaches of Clauses 7.2 and 7.3. The appeal on this point was successful.

The Appeal Board noted all the rulings regarding Section 2 of the formulary pack and did not consider that Novo Nordisk had failed to maintain high standards. The Appeal Board ruled no breach of Clause 9.1. The appeal on this point was successful.

Section 3 - 'Health economic evaluation'

COMPLAINT

Section 3.1 introduced cost-efficacy claims in support of Victoza with respect to weight reduction and reduction in blood pressure. This invited the reader to consider the cost-benefit of liraglutide in the context of a licensed treatment for obesity and systolic hypertension; this was misleading and inconsistent with the SPC. Indeed, the fact that changes in systolic blood pressure and body mass index had been included as 'Clinical inputs' in the economic modelling to support the cost-effectiveness of Victoza was evidenced in Tables 3.2 and 3.3. This indicated that other payor materials using this flawed economic modelling were also in breach of the Code. The rationale supporting the claim of a favourable cost implication of initiating Victoza and the need for self-monitoring of blood glucose (SMBG) was flawed, misleading and inconsistent with the Victoza SPC and real-life clinical practice.

Section 3.6 again misled by using the wording '… any time of day ...' with regard to the precise posology and method of administration as defined in the Victoza SPC. The reader was also invited to consider the cost advantage conferred by Victoza in that, when it was combined with oral antidiabetic agents the need for self monitoring of blood glucose was somehow negated.

The stand-alone statement that 'SMBG is not needed in order to adjust the dose of liraglutide' was inconsistent with the SPC with regard to the need for SMBG when combining treatment with a sulphonylurea. Further, the statement that 'Therefore, initiating liraglutide before a treatment that does require SMBG will have a favourable cost implication' seemed to ignore the fact that the majority of patients would already be on treatments that required SMBG when Victoza was started; the latter reflected the real-life clinical situation where Victoza was an add-on treatment to metformin and/or sulphonylurea, not vice-versa as was misleadingly implied by Novo Nordisk.

Section 3.8 discussed the numbers needed to treat (NNT) associated with liraglutide and invited a comparison with other antidiabetic agents as depicted in Figure 3.5. The calculation of the liraglutide NNT involves employing a composite endpoint which included reduction in SBP and no weight gain. Liraglutide was not licensed to reduce systolic blood pressure or weight and as such the NNT of 'four' was derived on a false premise; this was misleading and inconsistent with the liraglutide SPC.

For the reasons outlined above Lilly alleged that these four Sections were in breach of Clauses 2, 3.2, 7.2, 7.3, 7.4, 7.8, 7.9, 7.10, 8.1, 9.1 and 10.2 of the Code.

RESPONSE

Section 3.1: Novo Nordisk submitted that the value of any antihyperglycaemic agent both from a clinical and cost-effectiveness perspective could only be evaluated properly if effects and side-effects or elimination of side-effects were all considered. Thus mentioning the additional benefits of no weight gain, and systolic blood pressure provided a full evaluation and was as such, acceptable. Novo Nordisk did not agree that this section would imply that liraglutide had licensed indications other than that of improving glycaemic control.

Section 3.6: Novo Nordisk submitted that it did not believe the statement that liraglutide could be used at any time of day was misleading. It was consistent with Section 4.2 of the Victoza SPC.

Novo Nordisk disagreed that the statement 'SMBG is not needed in order to adjust the dose of liraglutide' was inconsistent with the liraglutide SPC. Novo Nordisk was unclear as to the allegation that 'The reader was invited to consider the cost advantage conferred by Victoza in that, when it was combined with oral antidiabetic agents the need for SMBG was somehow negated'. It failed to see how this could be the interpretation of this clause. The only mention of oral antidiabetic agents was where it stated that 'oral medication has not been factored

into the cost-effective analysis' and where examples of the number of SMBG tests were recommended, where SMBG tests were clearly recommended.

Novo Nordisk disagreed with Lilly's allegation that the statement 'initiating liraglutide before a treatment that does require SMBG will have a favourable cost implication' was misleading as it did not reflect the true clinical situation. The purpose of this statement was to simply confirm, in the cost effectiveness analysis that if liraglutide **were to be** initiated before a treatment that required SMBG, there would be a cost benefit. It was a hypothetical analysis, and as such, not misleading.

Section 3.8: As to the allegation concerning weight reduction, Novo Nordisk referred to its response in point D2 above to Sections 2.1, and 2.5.2, and 2.5.3 of Section 2 and its response in relation to points B3 and B4 above.

PANEL RULING

The Panel noted from Novo Nordisk's submission that mentioning the additional benefits of no weight gain and systolic blood pressure provided a full evaluation and was acceptable. The Panel noted that Section 3.1 included the claims that liraglutide was 'cost-effective compared with glimepiride when added to metformin monotherapy (cost/QALY £23,598), and with rosiglitazone when added to glimepiride monotherapy (cost/QALY £10,751)'. The basis for these calculations was given in Tables 3.2 and 3.3. The clinical inputs 'Change in HbA1c', 'Change in SBP' and 'Change in BMI' were listed in each table. Table 3.2 was based on a sub group of patients from Nauck *et al* (LEAD 2). The BMI data was not given in Nauck *et al* (LEAD 2). The Panel noted the comments it had made about Nauck *et al* (LEAD 2) in Point B1 above.

Table 3.3 was based on a sub group of patients from LEAD 1.

The Panel considered that Tables 3.2 and 3.3 implied that the indications for Victoza included decreasing weight and systolic blood pressure. This was not so. Section 3.1 of the formulary pack did not make the licensed indication clear nor the magnitude of the weight reduction and blood pressure data. The material was incomplete thus misleading as alleged and a breach of Clauses 7.2 and 7.3 was ruled. These rulings were appealed.

The Panel considered that, in the context of a health economic evaluation, Section 3.6 was not misleading with regard to the administration of Victoza. In the Panel's view the important consideration was the once-daily administration of Victoza. That the SPC further advised that it had to be administered at about the same, convenient time each day was not important in terms of an economic evaluation. No breach of Clauses 3.2 and 7.2 was ruled.

Section 3.6 stated that the cost of self monitoring of blood glucose was added where necessary. It also stated that 'SMBG is not needed in order to adjust the dose of liraglutide. Therefore initiating liraglutide before a treatment that does require SMBG will have a favourable cost implication'. The Panel noted Lilly's view that the statement appeared to ignore the fact that when Victoza was started the majority of patients would already be on treatments that required SMBG. The section implied that liraglutide would be used prior to a sulphonylurea. The Panel considered that there might be a theoretical cost benefit but this was not made clear. A breach of Clause 7.2 was ruled.

Section 3.8 'Number needed to treat one patient successfully to target' included results from a meta-analysis comparing patients treated to <7.0% HbA1c, <130mmHg SBP with no weight gain. The Panel noted that the composite endpoint had been made clear and was relevant to diabetic patients. The SPC included data for changes in weight and blood pressure. It would have been interesting to include the data purely for the licensed indication ie reduction in HbA1c. The Panel considered that this section was not misleading with regard to the licensed indication as alleged. No breach of Clauses 3.2 and 7.2 was ruled.

The Panel noted that Lilly had alleged a breach of Clauses 7.8 and 10.2 of the Code without giving any details of what was the subject of the allegations. In the circumstances the Panel considered that insufficient detail had been provided by Lilly and thus no breach of Clauses 7.8 and 10.2 was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. This ruling was appealed. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that Section 3 was focused on the health economy of Victoza. In order to evaluate the cost-effectiveness of a medicine the applied model should consider changes in the clinically relevant parameters triggered by the medicine. The decision whether a compound was cost-effective in type 2 diabetes did not depend purely on its efficacy (ie improving HbA1c) but also on the additional benefits that the medicine could provide. Tables 3.2 and 3.3 listed the components of the health economy model. In this context, the tables did not imply the indication of a medicine, but the clinically relevant components of the model on the basis of which different stakeholders could make decisions about cost-effectiveness. Novo Nordisk submitted that the relevant target group of the formulary pack (such as budget holders) would not draw conclusions from the components of a health economy model in terms of the licensed indication of the medicine. Furthermore, it was reasonable to assume that they also read the

clinical summary of Victoza (Section 2) which clearly stated the licensed indication of the product (as discussed in point D2 above).

On the basis of the above Novo Nordisk did not agree with the Panel that Tables 3.2 and 3.3 were in breach of Clauses 7.2 and 7.3 of the Code.

Novo Nordisk submitted that as it had appealed all but one of the breaches ruled by the Panel, it did not agree that high standards had not been maintained and it therefore appealed the Panel's ruling in this regard.

APPEAL BOARD RULING

The Appeal Board noted that Section 3 was a 'Health Economic Evaluation'. The comparisons in Tables 3.2 and 3.3 were consistent with a health economic evaluation which would look at all of the benefits of the medicine including in this instance changes in weight and systolic blood pressure. The Appeal Board considered that Tables 3.2 and 3.3 did not mislead as to the indications for Victoza they reflected the relevant factors about its cost effectiveness. No breach of Clauses 7.2 and 7.3 was ruled. The appeal on this point was successful.

The Appeal Board noted all the rulings regarding Section 3 of the formulary pack and did not consider that Novo Nordisk had failed to maintain high standards. The Appeal Board ruled no breach of Clause 9.1. The appeal on this point was successful.

* * * * *

At the completion of its consideration of this case, the Appeal Board was concerned about the presentation of the complaint. The Appeal Board deplored the way the complaint had been constructed with so many repetitive allegations. The response to the complaint could also have been better constructed; however some of the problems were as a direct result of the nature of the complaint. The time taken by the Panel and the Appeal Board to consider this case could have been substantially reduced if the complaint had been better presented.

Complaint received **9 October 2009**

Case completed **28 April 2010**

ANONYMOUS v ROCHE

Promotion of Xenical

An anonymous and non-contactable complainant alleged that Roche Products had used payments to induce prescribing of Xenical (orlistat). In particular a named chemist chain had been paid £100,000 per year, to ensure Xenical was prescribed directly to patients via patient group directions (PGDs).

The complainant provided a copy of an email, sent in November, 2008, which referred to an email and a Xenical sales agreement highlighting a cumulative shortfall in payment from Roche for an identified sum.

The detailed response from Roche is given below.

The Panel noted that the complainant had provided very little information to support their allegation. A complainant had the burden of proving their complaint on the balance of probabilities.

Roche had denied that it had paid the chemist chain £100,000 per year as alleged but stated that it had, however, paid £100,000 in 2007 as a one-off contribution towards the cost of updating material pursuant to a change in policy by Roche. Roche also stated that this contribution would help restore the margin on sales that would have achieved without the additional overhead. Given the specific reference to £100,000 by the complainant, it was extremely disappointing that Roche did not refer to this one-off payment in its initial response. To wait until asked for further information was poor practice. Self-regulation, and the reputation of the industry in that regard, relied upon full and frank disclosure at the outset.

The Panel noted that Roche viewed the one-off payment as an arrangement concerning measures or trade practices relating to prices, margins or discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993 and, therefore, outside the scope of the Code. The Panel disagreed. Prices, margins and discounts were financial terms and in the Panel's view had to be directly linked to the volume or cost of a product or products purchased. The £100,000 payment was a contribution to the cost of updating weight-loss programme materials. The Panel considered that this payment could not take the benefit of the exemption from the Code afforded to trade practices and was thus within the scope of the Code. Although concerned about the impression given by the one-off payment of £100,000 the Panel did not have any information before it to show that it had been used to ensure that Xenical was prescribed directly to patients via PGDs. No breach of the Code was ruled.

An anonymous and non-contactable complainant complained about the promotion of Xenical (orlistat) by Roche Products Limited.

COMPLAINT

The complainant stated that Roche had used payments to induce prescribing. In particular a named chemist chain had been paid £100,000 per year to ensure Xenical was prescribed directly to patients via patient group directions (PGDs).

The complainant provided a copy of an email, sent in November, 2008, which referred to an email and a Xenical sales agreement highlighting a cumulative shortfall in payment from Roche for an identified sum.

When writing to Roche, the Authority noted that it was not clear as to whether the complaint came within the scope of the Code. Roche was asked to deal with this point in its response and to bear in mind the requirements of Clauses 2, 9.1 and 18.1 of the Code.

RESPONSE

Roche stated that it took any complaint relating to its compliance with the Code very seriously. Notwithstanding this, Roche requested that the Panel dismiss the complaint on the basis that the complainant had not provided any evidence to support the complaint and, as a result, the burden of proof had not been satisfied. Roche also requested that, when considering the complaint, the Panel should take into account the fact that the complainant was anonymous and it had not been established if the complainant had any commercial, financial or other interest in the matter of the complaint or in Roche.

Without prejudice to these requests, Roche recognised that the Authority was obliged to investigate complaints that it received that were related to the Code. Roche was committed to assisting the Authority in this regard including assisting in investigations such as those raised in this complaint.

Copies of the sales agreement and Xenical SPC were provided. However, Roche could not locate copies of the email chains referred to in the complaint, thus copies were not provided.

Was the complaint within the scope of the Code?

Roche submitted that the arrangements did not come within the scope of the Code as they were 'measures or trade practices relating to prices, margins or discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993', as set out in Clause 1.2.

Prescription of Xenical by PGD

Roche explained that PGDs were written instructions for the supply or administration of medicines to groups of patients who might not be individually identified before presentation for treatment. PGDs must be signed by a senior doctor and a pharmacist both of whom should have been involved in developing the direction. A PGD must also be authorised by an appropriate regulatory body as set out in the legislation applying to PGDs. As a result, a PGD could be used to allow an authorised person to supply or administer prescription only medicines to patients without necessarily referring back to a doctor for an individual prescription.

The chemist chain operated a weight-loss programme. Roche understood that, as part of this programme, Xenical was prescribed using a private PGD. Under these arrangements patients paid for their treatment rather than obtaining it via an NHS prescription. The chemist chain was responsible for the development of this PGD and the content of the weight-loss programme. The arrangements pre-dated the availability of OTC orlistat and related solely to Xenical.

Payment of £100,000

Roche submitted that it did not pay £100,000 to ensure the prescription of Xenical via PGDs. However, £100,000 was paid in 2007 as a financial contribution to the costs the chemist chain would incur in updating weight-loss programme materials consequential to a change of policy by Roche in relation to patient support activities.

Roche explained that it operated a support service for Xenical patients, referred to as MAP (motivation, advice, pro-active support). The service was intended to provide advice on Xenical and how it worked and also information on healthy eating. This service was for the benefit of any patient, not just those enrolled on the chemist chain's weight-loss programme. Previously, booklets and advice sheets were posted to patients periodically. The service was switched to a web-based system, EMAP, during 2006.

The chemist chain had to inform its existing patients of the change to EMAP and to alter its communications materials given to new patients as a result of Roche switching to the EMAP service. The chemist chain had not known that it would incur these costs when it established its weight-loss programme. Roche agreed to contribute £100,000 to assist as an acknowledgement that additional costs had arisen only because Roche had switched to the EMAP service. The content of the communications was determined by the chemist chain and the £100,000 was not conditional on any content changes being approved by Roche. The payment did not benefit individual pharmacists, but helped restore the margin on sales.

Roche submitted that the above payment was possibly the payment referred to by the complainant. However, the payment was not made to ensure the prescription of Xenical via PGDs and was not paid annually as alleged. The payment was a one-off, paid as part of a commercial arrangement to recognise additional unforeseen costs as a result of a change in Roche's internal systems. For the purpose of the Code, Roche viewed the payment as an arrangement relating to measures or trade practices relating to prices, margins or discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993 and, therefore, outside the scope of the Code.

PANEL RULING

The Panel noted that the complainant had provided very little information to support their allegations. The Constitution and Procedure stated that a complainant had the burden of proving their complaint on the balance of probabilities. The complainant was anonymous and non-contactable and so could not be asked to supply further details.

Roche had denied that it had paid £100,000 per year as alleged but stated that it had, however, paid the chemist chain £100,000 in 2007 as a one-off contribution towards the cost of updating material pursuant to a change in policy by Roche. Roche also stated that this contribution would help restore the margin on sales that would have been achieved without the additional overhead. Given the specific reference to £100,000 by the complainant, it was extremely disappointing that Roche did not refer to this one-off payment in its initial response. To wait until asked for further information was poor practice. Self-regulation, and the reputation of the industry in that regard, relied upon full and frank disclosure at the outset.

The Panel noted that, for the purposes of the Code, Roche viewed the one-off payment as an arrangement concerning measures or trade practices relating to prices, margins or discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993 and, therefore, outside the scope of the Code. The Panel disagreed. Prices, margins and discounts were financial terms and in the Panel's view had to be directly linked to the volume or cost of a product or products purchased. The £100,000 payment was a contribution to the cost of updating weight-loss programme materials. The Panel considered that this payment could not take the benefit of the exemption from the Code afforded to trade practices and was thus within the scope of the Code. Although concerned about the impression given by the one-off payment of £100,000 the Panel did not have any information before it to show that it had been used to ensure that Xenical was prescribed directly to patients via PGDs. No breach of Clause 18.1 was ruled.

Complaint received **19 November 2009**

Case completed **10 February 2010**

PRESCRIBING ADVISOR v BOEHRINGER INGELHEIM

Promotion of Pradaxa

A prescribing advisor alleged that Boehringer Ingelheim had promoted unlicensed doses of Pradaxa (dabigatran) in breach of the Code.

The use of Pradaxa had been restricted to the orthopaedic unit at the complainant's local hospital. The complainant provided a copy of a letter, dated October 2009 and signed by three consultant orthopaedic surgeons, which stated:

> **'In orthopaedics, as you know, for years we have used Enoxaparin 20. Recently we converted to Pradaxa and have had a significant number of leaky orthopaedic wounds and 2 rectal bleeds.**
>
> **On unofficial advice from Pradaxa reps we reduced Pradaxa to half dosage, however this is unlicensed'.**

The detailed response from Boehringer Ingelheim is given below. It was sent to the complainant for comment prior to the Panel making a ruling.

The Panel noted that the recommended dose of Pradaxa was 220mg daily taken as 2 capsules of 110mg. Treatment should be initiated orally within 1-4 hours of completed surgery (total hip or knee replacement) with a single capsule. Two capsules were to be given thereafter once daily for a total of 10 days.

The Panel noted the complainant's statement that 'several consultant surgeons contacted the company' apparently as a result of a number of patients developing bleeds whilst on Pradaxa. The letter, signed by three consultant orthopaedic surgeons, and referred to above, gave no details to identify the 'Pradaxa reps'; it was not known where, when or in what context information about the apparent routine use of half doses of Pradaxa had been given nor was it certain if the consultants' use of 'reps' meant medical (sales) representatives or someone else representing Boehringer Ingelheim. It was not known if the information had been provided in response to an unsolicited enquiry, although this was unlikely given that there was no record to show that it had been via Boehringer Ingelheim's medical information department.

Boehringer Ingelheim did not know which consultants had signed the letter of 20 October. Neither of the two medical representatives who covered the hospital at issue had discussed the use of half dose Pradaxa with the orthopaedic staff. As part of a discussion about bleeds in a patient aged over 75, representative one had discussed the use of a reduced dose of Pradaxa in patients in that age group (150mg/day vs 220mg/day). That representative had not covered the hospital after July 2009. The representative responsible for the hospital after that date had not discussed the use of half doses of Pradaxa and, when the complaint was received, had had little contact with the orthopaedic department.

Representatives' briefing material clearly stated that Pradaxa had two fixed doses – a standard dose (220mg/day) and a lower dose (150mg/day) for special patient populations. Promotional material similarly referred to these two doses. The Panel was concerned to note, however, that in May 2009 the sales force was briefed about inter-company correspondence in which a competitor had asserted that the Pradaxa field force had promoted choice and flexibility of dose. Representatives had been reminded to promote 220mg as the main dose of Pradaxa and that the 150mg dose continued to be discussed within the context of special patient populations.

On the basis of the evidence before it, the Panel considered that it was impossible to know what had transpired. The complainant had the burden of proving their complaint on the balance of probabilities. It seemed clear that the consultants had discussed half dose Pradaxa with someone from Boehringer Ingelheim whose identity was not known, neither was the context in which the conversation had taken place known. However both parties assumed that it was likely to have been sales representatives. A lower dose was licensed for special patient populations. Half dose Pradaxa, except within four hours of surgery, was unlicensed. This was not the first time it had been asserted that Boehringer Ingelheim representatives had promoted unlicensed doses. A judgement had to be made on the available evidence in the present case bearing in mind the extreme dissatisfaction usually necessary on the part of an individual before he or she was moved to submit a complaint. The Panel was very concerned about the matter. On balance, it considered that on the basis of the evidence provided by the parties the circumstances were such that breaches of the Code could not be ruled.

Following its consideration of this complaint the Panel considered that Boehringer Ingelheim would be well advised to remind its representatives of the need to be extremely clear about the dose of Pradaxa.

A prescribing advisor complained about the promotion of Pradaxa (dabigatran) by Boehringer Ingelheim Limited.

COMPLAINT

The complainant noted that Pradaxa was approved for use for its licensed indications and at licensed doses in summer 2008. Its use had been restricted to the orthopaedic unit at the complainant's local hospital. It was noted since approval that a number of patients developed bleeds whilst on this medicine. Several consultant surgeons contacted the company whose representatives advised them 'unofficially' that it could be used at 'half dose'. The consultants had not sought the advice of the hospital pharmacy medicines information department. The complainant had a letter from the consultants confirming the above; the letter was subsequently provided in response to a request from the Authority. The letter, dated 20 October 2009 and headed 'DVT prophylaxis', began:

> 'In orthopaedics, as you know, for years we have used Enoxaparin 20. Recently we converted to Pradaxa and have had a significant number of leaky orthopaedic wounds and 2 rectal bleeds.
>
> On unofficial advice from Pradaxa reps we reduced Pradaxa to half dosage, however this is unlicensed'.

The complainant alleged that the advice to use Pradaxa at an unlicensed dose might be in breach of the Code.

When writing to Boehringer Ingelheim the Authority asked it to respond in relation to the requirements of Clauses 3.2, 15.2 and 15.9 of the Code.

RESPONSE

Boehringer Ingelheim emphasised that it was committed to operating in a responsible, ethical and professional manner and it strove through its activities and materials to maintain high standards and strengthen the image of the pharmaceutical industry. Therefore, it was surprised and disappointed to have received the complaint which related to the conduct of its field force.

Boehringer Ingelheim understood that an anonymous consultant orthopaedic surgeon at a named hospital claimed to have contacted an undisclosed number of Boehringer Ingelheim representatives for advice about a problem with some of his patients rather than approaching the hospital's medicines information department for advice. In the consultant's view, the advice received recommended the use of Pradaxa at an unlicensed dose. The complaint was from another anonymous employee of the same hospital.

Boehringer Ingelheim submitted that it was not clear from the letter when and where the alleged 'off-label' advice was given by its representative and without further information from the complainant it was difficult to investigate the allegations completely. However, Boehringer Ingelheim had investigated the matter thoroughly given the information provided.

Boehringer Ingelheim submitted that since the launch of Pradaxa in April 2008 there had been no medical information requests from the hospital in question and therefore it assumed that the complaint related to its representative specifically responsible for that hospital. Two representatives had covered the hospital (representative 1 until 1 July 2009; representative 2 after 1 July 2009). Each representative had been asked about their communication and contact with any health professionals at the hospital during their work.

Representative 1

- April 2009: met an orthopaedic consultant and presented to the pharmacy department when the correct dosing regime for Pradaxa was clarified.
- May 2009: met three consultants in anaesthetics. Also met another to discuss orthopaedic nurse training. During this meeting the representative was informed of a bleed with Pradaxa at the higher licensed dose in patient over the age of 75. The representative immediately communicated the correct dosing regime with all key personnel. The summary of products characteristics (SPC) stated 'In elderly patients (>75 years) there is limited clinical experience. The patients should be treated with caution. The recommended dose is 150mg taken once daily as 2 capsules of 75mg (see Section 4.4 and 5.1)'.
- The representative did not state that half dosing for Pradaxa could be used.
- No medical information requests were received following on from these calls.

Representative 2

- July 2009: met one orthopaedic consultant but did not discuss halving the dose of Pradaxa
- The orthopaedic department cancelled a meeting scheduled for November 2009.
- Since the meeting in July the representative had had no communication with the department.
- The representative had never been in face-to-face communication with the hospital's pharmacy; however, Pradaxa patient information cards and Pradaxa dosing cards were left upon request.

Boehringer Ingelheim submitted that orthopaedic consultants from the hospital attended the British Orthopaedic Association Annual Conference in September 2009, however there was no record of any medical information request on the dosing of Pradaxa from them. The consultant's letter appeared to have been written after this conference.

Boehringer Ingelheim stated that its representatives had acted with the highest standard of ethical conduct in the discharge of their duties and therefore complied with all relevant requirements of the Code. Boehringer Ingelheim therefore submitted that it was not in breach of Clause 15.2.

Boehringer Ingelheim submitted that its representative training and briefing materials clearly did not advocate any course of action which would be likely to be a breach of the Code. Neither the current Pradaxa detail aid nor its briefing for use referred to the licensed use of a half dose of Pradaxa, except on the day of surgery for its initial dose. Similarly the scientific support aid for representatives' use during calls did not refer to the licensed use of a half dose of Pradaxa, except on the day of surgery for its initial dose.

Boehringer Ingelheim submitted that it had never produced material that referred to a lower than usual dose of Pradaxa.

Boehringer Ingelheim provided a copy of the representatives' briefing material about how to handle 'off-label' enquiries, this was included in a proactive briefing to the representatives covering a press release of results of a clinical trial for an 'off-label' indication.

Boehringer Ingelheim also provided a copy of the email which covered a briefing that was sent to its sales team to clarify that its promotional materials, training and activities were consistent with the SPC.

Boehringer Ingelheim submitted that the materials and briefings provided clearly complied with the relevant requirements of the Code and did not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. Therefore, Boehringer Ingelheim denied a breach of Clause 15.9.

Boehringer Ingelheim further submitted that it had clearly demonstrated by the materials and briefings provided, and the conduct of its representatives, that the promotion of Pradaxa had been within the terms of the marketing authorization and consistent with the SPC. The company thus denied a breach of Clause 3.2.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant did not have any more information on the details of the advice ie who gave it and when. The complainant considered, however, that it must have been Boehringer Ingelheim sales staff and that they and their superiors must take ownership for it. The end result was that a significant portion of very vulnerable post total hip and total knee replacement patients were exposed to an unnecessary health risk by being discharged from hospital on sub-therapeutic treatment. The consequences of venous thromboembolism, both clinically diagnosed and un-diagnosed were poorly recognised and this advice exposed patients to risks that they did not deserve. Pradaxa was aggressively marketed locally and it was disappointing that Boehringer Ingelheim would not take ownership of poor advice from its representatives.

PANEL RULING

The Panel noted that the recommended dose of Pradaxa was 220mg daily taken as 2 capsules of 110mg. Treatment should be initiated orally within 1-4 hours of completed surgery (total hip or knee replacement) with a single capsule. Two capsules were to be given thereafter once daily for a total of 10 days.

The Panel noted the complainant's statement that 'several consultant surgeons contacted the company' apparently as a result of a number of patients developing bleeds whilst on Pradaxa. The complainant had provided a copy of a letter, dated 20 October 2009 and signed by three consultant orthopaedic surgeons, which stated 'On unofficial advice from Pradaxa reps we reduced Pradaxa to half dosage, however this is unlicensed'. No details had been provided to identify the 'Pradaxa reps'; it was not known where, when or in what context information about the apparent routine use of half doses of Pradaxa had been given nor was it certain if the consultants' use of 'reps' meant medical (sales) representatives or someone else representing Boehringer Ingelheim. It was not known if the information had been provided in response to an unsolicited enquiry, although this was unlikely given that there was no record to show that it had been via Boehringer Ingelheim's medical information department.

Boehringer Ingelheim did not know which consultants had signed the letter of 20 October. Neither of the two medical representatives who covered the hospital at issue had discussed the use of half dose Pradaxa with the orthopaedic staff. As part of a discussion about bleeds in a patient aged over 75, representative one had discussed the use of a reduced dose of Pradaxa in patients in that age group (150mg/day vs 220mg/day). That representative had not covered the hospital after July 2009. The representative responsible for the hospital after that date had not discussed the use of half doses of Pradaxa and, when the complaint was received, had had little contact with the orthopaedic department.

Representatives' briefing material clearly stated that Pradaxa had two fixed doses – a standard dose (220mg/day) and a lower dose (150mg/day) for special patient populations. Promotional material similarly referred to these two doses. The Panel was concerned to note, however, that in May 2009 the sales force was briefed about inter-company correspondence in which a competitor had asserted that the Pradaxa field force had promoted choice and flexibility of dose. Representatives had been reminded to promote 220mg as the main dose of Pradaxa and that the 150mg dose continued to be discussed within the context of special patient populations.

On the basis of the evidence before it, the Panel considered that it was impossible to know what had transpired. The complainant had the burden of

proving their complaint on the balance of probabilities. It seemed clear that the consultants had discussed half dose Pradaxa with someone from Boehringer Ingelheim whose identity was not known, neither was the context in which the conversation had taken place known. However both parties assumed that it was likely to have been sales representatives. A lower dose was licensed for special patient populations. Half dose Pradaxa, except within four hours of surgery, was unlicensed. This was not the first time it had been asserted that Boehringer Ingelheim representatives had promoted unlicensed doses. A judgement had to be made on the available evidence in the present case bearing in mind the extreme dissatisfaction usually necessary on the part of an individual before he or she was moved to submit a complaint. The Panel was very concerned about the matter. On balance, it considered that on the basis of the evidence provided by the parties the circumstances were such that breaches of the Code could not be ruled. Thus the Panel ruled no breach of Clauses 3.2, 15.2 and 15.9.

Following its consideration of this complaint the Panel considered that Boehringer Ingelheim would be well advised to remind its representatives of the need to be extremely clear about the dose of Pradaxa.

Complaint received **26 November 2009**

Case completed **29 April 2010**

PRIMARY CARE TRUST SENIOR PHARMACIST v FLYNN PHARMA

Distaclor MR email

The senior pharmacist at a primary care trust (PCT) complained about the promotion of the antibiotic Distaclor MR (extended release cefaclor) by Flynn Pharma in an unsolicited email which had been sent to a local named GP. In particular the local medicines management team was concerned that prescribers were offered six free starter packs of Distaclor. The Department of Health (DoH) guidance on the supply of medicines out-of-hours services stated that a full course of medicines should be supplied as appropriate to the presenting condition; the supply of starter packs was not appropriate.

The detailed response from Flynn is given below.

Flynn did not know the identity of the GP but submitted that the email was sent via a third party provider which made it clear at the outset to those NHS employees that agreed to go on the database that they would be sent promotional material from pharmaceutical companies. In the absence of any detailed information from the complainant and in the light of Flynn's submission the Panel ruled no breach of the Code.

The Code allowed starter packs for a primary care prescriber to initiate treatment when there might be an undesirable or unavoidable delay in having a prescription dispensed. The amount should be sufficient to tide a patient over until their prescription could be dispensed. Antibiotics were listed as an example of a medicine that might be provided as a starter pack.

The Panel noted the DoH's advice that the supply of starter packs was not appropriate. There might be occasions where the prescriber could not dispense a full course and in the limited circumstances outlined in the Code the supply of a starter pack was helpful when it was in the patient's best interest to start treatment as soon as possible.

Although not supported by the DoH advice, the Panel did not consider that the principle of offering starter packs of an antibiotic breached the Code as alleged. It might be argued that the offer of a starter pack was presented in the email at issue as the main reason for using Distaclor. However the Panel did not consider that in this regard the email failed to promote the rational use of Distaclor and no breach of the Code was ruled. The company had not failed to maintain high standards.

The senior pharmacist at a primary care trust (PCT), complained about the promotion of the antibiotic Distaclor MR (extended release cefaclor) by Flynn Pharma Ltd in an unsolicited email which had been sent to a local GP.

COMPLAINT

The complainant stated that the local medicines management team was concerned about the email which appeared to breach the Code. In particular the team was concerned that prescribers were offered six free starter packs of Distaclor. The Department of Health (DoH) guidance on out-of-hours services, 'Securing proper access to medicines in the out-of-hours period' stated in section 2.8 that:

> 'Where medicines are supplied out-of-hours it should be a full course as appropriate to the presenting condition, i.e. the amount that would otherwise have been prescribed. The supply of starter packs is not appropriate.'

When writing to Flynn, the Authority asked it to respond in relation to Clauses 7.10, 9.1 and 9.9 of the Code.

RESPONSE

Flynn stated that in common with many other companies, it retained the services of a third party provider to contact relevant NHS recipients, the records for which were maintained on a database of NHS employees. All such NHS employees had been previously contacted by the provider as part of a validation process.

During the first contact the provider identified itself and outlined what it was, what it did, and the need for an email address in order to allocate an access code to its NHS online directory service. The NHS employee was informed that they might from time to time receive communications from one of the provider's associated/affiliated companies which would be relevant to their medical or non medical specialisation or administrative responsibilities. The communication was along the lines of '[the provider] will from time to time send information by email about our associated/affiliated companies and their clients' product and services, which may include updates on specialist services, conferences and seminars, diagnostic, medical and pharmaceutical promotional materials as well as official information'.

A follow-up email to the NHS employee confirmed the points raised and the access code. This email also invited comment from the recipient and asked them to make contact if they needed to amend any of the information held. It also reiterated that they would be sent information about products and services along with other medical and non-medical information.

In order to ensure that only those recipients who wished to receive such material did so there was an opt-out facility on all the provider's emails (the footnote on the promotional item in question referred).

The provider regularly re-evaluated its opt-in procedures.

Finally, Flynn noted that Cases AUTH/2111/3/08 and AUTH/2112/3/08 dealt with the same issue (alleged unsolicited email) and in both no breach was ruled. The point at issue in the present case was fundamentally the same. The Distaclor MR email had not been unsolicited and recipients had given prior, fully informed consent to receive promotional emails on behalf of pharmaceutical companies. Thus, Flynn respectfully submitted that there was no breach of Clause 9.9.

In regard to the second matter, the complainant had noted advice contained in a 'practical guide' previously issued by the DoH for PCTs and organised providers entitled 'Delivering the Out-of-Hours Review. Securing Proper Access to Medicines in the Out-of-Hours Period' (Gateway Number 4107). Specifically the complainant cited Section 2.8 which advised that 'where medicines are supplied out-of-hours, it should be a full course as appropriate to the presenting condition .... The supply of starter packs is not appropriate'. Flynn was not previously aware of this guidance which it understood was issued in 2005.

The DoH advice was just that – advice – and health professionals and other interested stakeholders (where they were aware) should and would, generally take it into account and apply it wherever possible and practicable. It did not, however, carry the force of regulation or statutory authority and allowed proper authority for prescribers to not follow such advice where they considered circumstances dictated. Flynn submitted that there were circumstances in which a prescriber might wish or need to issue a starter pack to initiate treatment pending the dispensing of a complete prescription by a pharmacy. Notwithstanding the sound intent and principles of the DoH advice, Flynn considered that there were situations in which it was not possible for the prescriber to both prescribe and dispense a full course of treatment. The promotional email at issue specifically referred to service provision 'out-of-hours or when the local pharmacy is closed'. Issues of prescription payment, processing and reimbursement came to mind, amongst others which, in Flynn's view, had not been considered in the DoH advice.
The DoH advice had not been widely promulgated and indeed the Code itself, in both the 2006 and 2008 editions, referred to starter packs in the supplementary information to Clause 17, which was at variance with the DoH advice. Specifically, the Code advised that:

> 'Starter packs are small packs designed to provide sufficient medicine for a primary care prescriber to initiate treatment in such circumstances as a call out in the night or in other instances where there might be some undesirable delay in having a prescription dispensed. It follows from this that the types of medicines for which starter packs are appropriate are limited to those where immediate commencement of treatment is necessary or desirable, such as analgesics or antibiotics.'

Thus in two successive versions of the Code which had been issued after the DoH had published its advice, explicit reference was made to antibiotic starter packs and it was entirely reasonable that a supplier might be influenced and directed by information set out in the Code. Whilst there were relevant arguments, on both sides, as to the extent to which the supply of antibiotic starter packs constituted 'best practice', it was not a prohibited activity and nor did it breach the Code's 'high standards' test (Clause 9.1), the prime intent of which in any event was concerned with matters of suitability and taste, which did not appear to be at issue here.

Flynn assumed that the Authority's reference to Clause 7.10 was in the context of the importance of taking and completing a full prescribed course of antibiotics. Clearly this objective was not achieved by taking only the two doses available in the Distaclor MR starter pack. A directive to take a complete course of treatment was however clearly included in the patient leaflet accompanying the starter pack and in the prescribing information which was electronically linked to the promotional email. Thus, Flynn respectfully maintained that it had taken proper account of the product's risk/benefit profile in terms of prescriber and patient directions as to the importance of taking a full course of treatment as prescribed. Although not subject to or referenced in this complaint, the claims made in the email were consistent with the licensed indications and known evidence as to both the safety and efficacy of Distaclor MR.

In response to a request for further information, Flynn provided a copy of the mailing sent to NHS employees and issued by the provider. This was underpinned by the provider's internal opt-in policy which was regularly reviewed. Although this was not issued to health professionals, it provided relevant guidance as to the standards and controls applied. Relevant abstracts from the policy statement were provided.

PANEL RULING

The complainant had complained that the email was sent unsolicited to a named GP. Flynn did not know the identity of that GP. Flynn submitted that the email was sent via a provider which maintained a database of NHS employees and made it clear at the outset to those that agreed to go on the database that they would be sent promotional material from pharmaceutical companies. In the absence of any detailed information from the complainant and in the light of Flynn's submission the Panel ruled no breach of Clause 9.9.

With regard to the supply of starter packs the Panel noted that Clause 17 allowed starter packs for a primary care prescriber to initiate treatment when there might be an undesirable or unavoidable delay in having a prescription dispensed. The amount should be sufficient to tide a patient over until their prescription could be dispensed. The supplementary information to the Code specifically cited antibiotics as an example of a medicine that might be provided as a starter pack.

The Panel noted the DoH document and its advice that the supply of starter packs was not appropriate. There might be occasions where the prescriber could not dispense a full course and in the limited circumstances outlined in the Code the supply of a starter pack was helpful when it was in the patient's best interest to start treatment as soon as possible.

Although not supported by the DoH advice, the Panel did not consider that the principle of offering starter packs of an antibiotic was in breach of the Code as alleged. It might be argued that the offer of a starter pack was presented in the email at issue as the main reason for using Distaclor. However the Panel did not consider that in this regard the email failed to promote the rational use of Distaclor and no breach of Clause 7.10 was ruled. The company had not failed to maintain high standards and no breach of Clause 9.1 was ruled.

Complaint received **3 December 2009**

Case completed **19 February 2010**

CASE AUTH/2287/12/09 & AUTH/2288/12/09

DOCTOR v ROCHE and CHUGAI PHARMA

Journal supplement

A doctor complained about a supplement, 'Rheumatoid arthritis – from policy to action', that appeared in the Health Service Journal (HSJ), 10 December 2009. The back cover of the supplement carried an advertisement for RoActemara (tocilizumab) which was co-promoted by Roche and Chugai.

The complainant noted that, as stated in the supplement, Roche and Chugai had sponsored its development and distribution, and checked it for factual accuracy; they had also paid the author of the articles via the journal. The complainant alleged that the supplement, which was stapled inside the journal, was completely indistinguishable from independent editorial matter. The supplement used exactly the same house style as the HSJ and so readers who opened the journal at one of the supplement's pages would not know that it was promotional material.

The detailed response from Roche and Chugai is given below.

The Panel noted that Roche and Chugai had paid for the writing, printing and distribution of the supplement. The supplement was intended to be provided as a separate item but was instead stapled into the centre of the HSJ.

The Panel noted that the HSJ was written in four columns per page and each left hand page was colour coded in the top left hand corner to denote the section of the journal ie news (red), opinion (blue) etc. The supplement was presented in three columns per page and there was no colour coding of the left hand pages. The Panel thus did not consider that the supplement used exactly the same house style as the HSJ; it was not completely indistinguishable from the journal's independent editorial matter. That a sponsored supplement was bound in rather than loose did not *ipso facto* mean that its nature was disguised. The overall impression given to readers was the most relevant factor. A clear declaration of sponsorship appeared on the front cover. Further details were also provided on the inside front cover, beneath the index. The Panel considered that the supplement could be distinguished from the independent editorial matter and so was not disguised in that regard; no breach of the Code was ruled.

Upon appeal by the complainant, the Appeal Board noted that contrary to verbal information provided to Roche by its communications agency, the supplement had been stapled into the journal and not produced as a physically separate item as intended. In the Appeal Board's view this fundamentally changed the way in which readers would view it; many would flick through the journal, often from back to front, and might thus read one of the inside pages of the supplement without first seeing the declarations of sponsorship on what should have been the front cover and front inside cover. In the Appeal Board's view the inside pages of the supplement were not sufficiently dissimilar to the standard editorial text of the journal and so in that regard their nature was disguised. A breach of the Code was ruled as acknowledged by the companies.

A doctor complained about a 12 page rheumatology supplement, 'Rheumatoid arthritis – from policy to action', (ref ACTE00150W) that appeared in the Health Service Journal (HSJ), 10 December 2009. The back cover of the supplement carried an advertisement for RoActemara (tocilizumab) which was co-promoted by Roche Products Ltd and Chugai Pharma Europe Ltd.

COMPLAINT

The complainant noted that as stated on the inside front page of the supplement, the development and distribution of the supplement was sponsored, and checked for factual accuracy, by Roche and Chugai. It was further stated that the author of the articles was paid by Roche and Chugai via the Health Service Journal. The complainant noted that the supplementary information to Clause 12.1 of the Code stated that 'When a company pays for, or otherwise secures or arranges the publication of promotional material in journals, such material must not resemble independent editorial matter'. The complainant alleged that the supplement, which was stapled inside the journal, was completely indistinguishable from independent editorial matter. The supplement used exactly the same house style as the HSJ and so readers who opened the journal at one of the pages of the supplement would be unaware that it was promotional material.

When writing to Roche and Chugai the Authority asked them to respond in relation to the requirements of Clause 12.1 of the Code.

RESPONSE

Roche submitted a joint response on behalf of both companies.

The companies accepted the complainant's allegation of a breach of Clause 12.1. However,

whilst the companies recognised the complainant's concerns they stated that the intent was for the supplement to be an educational piece to provide the HSJ readers with an overview of rheumatoid arthritis policy through 2009.

The companies submitted that they had been verbally informed, by the communications agency facilitating the supplement, that the supplement would be separate ie not physically attached within the HSJ. There was no intention of disguising the supplement within the body content of the journal as the companies' sponsorship declaration was clear on both the outside and inside front cover in accordance with Clause 9.10.

The companies submitted that they had paid for the writing, printing and distribution of the supplement with full editorial control, with the author provided by the HSJ. Due to the full editorial control, and the inclusion of an advertisement, the supplement was certified in accordance with the companies' processes.

Although this was an inadvertent mistake, the companies submitted that they took any breach of the Code very seriously and were considering what action was required to ensure that this did not happen again.

PANEL RULING

The Panel noted that Roche and Chugai had paid for the writing, printing and distribution of the supplement. The supplement was intended to be provided as a separate item but was instead stapled into the centre of the HSJ.

The Panel noted that the text of the HSJ itself was written in four columns per page and each left hand page was colour coded in the top left hand corner to denote the section of the journal ie news (red), opinion (blue) etc. The text of the supplement in question was presented in three columns per page and there was no colour coding of the left hand pages. In that regard the Panel did not consider that the supplement used exactly the same house style as the HSJ as alleged; it was not completely indistinguishable from the journal's independent editorial matter. That a sponsored supplement was bound in rather than loose did not ipso facto mean that its nature was disguised. The overall impression given to readers was the most relevant factor. A clear declaration of sponsorship appeared on the front cover. Further details were also provided on the inside front cover, beneath the index. The Panel noted its comments above about the differences between the journal's house style and the supplement in question. The Panel considered that the appearance of the supplement was distinguishable from the independent editorial matter and the material was not disguised in that regard; no breach of Clause 12.1 was ruled.

APPEAL BY THE COMPLAINANT

The complainant submitted that the Panel had applied too narrow a definition of the term 'resemble' in this case. The complainant alleged that the rheumatology supplement was not distinguishable from the independent editorial content of the journal, in breach of Clause 12.1. The complainant noted that the companies agreed that they had breached the Code in that regard.

The complainant noted that the Panel had found some stylistic differences between the supplement and the rest of the journal ie that the supplement was written in 3-column format whereas the journal was in 4-column format and that the supplement lacked a coloured tab in the top left corner of the left-hand pages, which was present in the rest of the journal. Because of these two differences, the Panel correctly stated that the supplement was not completely 'indistinguishable' from the journal's independent editorial matter, since the supplement did not use 'exactly the same house style' as the rest of the journal. On this basis the Panel had ruled no breach of Clause 12.1. However, the wording of the supplementary information to Clause 12.1 stated that, 'When a company pays for, or otherwise secures or arranges the publication of promotional material in journals, such material must not resemble independent editorial matter'. The complainant submitted that the word 'resemble' was key. The Code did not stipulate that 'such material must not use exactly the same housestyle as the independent content'. Such a standard would be too undemanding since it could be met, for example, by using font size 11.5 rather than size 12. Rather, the Code stipulated a more stringent standard, namely that the content of the supplement must not 'resemble' independent editorial content. In the supplement in question, the colour scheme, typeface, graphics, spacing, justification, design of the text boxes and font size were identical to those of the rest of the journal. Moreover, until they were noted by the Panel, the complainant had not noticed the different number of columns nor the coloured tabs on the left hand pages - this despite being a regular subscriber to the Health Service Journal. Therefore the rheumatology supplement strongly resembled the independent editorial content. A typical reader who leafed through the journal and opened it on any of the inside pages of the supplement would not have noticed these subtle differences to set it apart from the independent editorial content. These inside pages, which included several self-contained 2-page articles, showed no indication that this was anything other than independent editorial content.

The complainant agreed with the Panel that the fact that a supplement was bound into a journal did not, ipso facto, imply that its nature was disguised. However, in such circumstances, the companies concerned needed to go out of their way to ensure that the supplement was distinct from the rest of the journal. This could be achieved, for example by using a completely different typeface (eg a serif font

vs sans-serif) and by including 'SPONSORED SUPPLEMENT' in bold type at the top of every page. To do anything less risked either misleading readers or raising a suspicion of an intent to deceive.

In summary the complainant alleged that the promotional material resembled independent editorial matter in breach of Clause 12.1.

COMMENTS FROM ROCHE AND CHUGAI

Roche submitted a joint response on behalf of both companies.

The companies noted in their response above that they had accepted the alleged breach of Clause 12.1 as the supplement was stapled into the HSJ and was not a separate item as originally intended and advised by their communications agency.

The companies reiterated that: the supplement was developed for educational purposes only; as such, the educational content was non-promotional and gave no commercial advantage to Roche and clear declarations of sponsorship were included to ensure the companies' involvement was not disguised.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant had no further comments.

APPEAL BOARD RULING

The Appeal Board noted that contrary to verbal information provided to Roche by its communications agency, regarding the presentation of the supplement, the supplement had been stapled into the centre of the HSJ and not produced as a physically separate item as intended. In the Appeal Board's view this fundamentally changed the way in which readers would view the supplement. The Appeal Board noted that many readers would flick through the journal, often from back to front, and might thus read one of the inside pages of the supplement without first seeing the declarations of sponsorship on what should have been the front cover and front inside cover. In the Appeal Board's view the inside pages of the supplement were not sufficiently dissimilar to the standard editorial text of the journal and so in that regard their nature was disguised. A breach of Clause 12.1 was ruled as acknowledged by the companies. The appeal was successful.

Complaint received **15 December 2009**

Case completed **25 March 2010**

CASE AUTH/2289/12/09

MERCK SHARP & DOHME v ALCON

Azarga leavepiece

Merck Sharp & Dohme alleged that a leavepiece which promoted the comfort of Azarga (brinzolamide/timolol eye drops) issued by Alcon Laboratories was not consistent with the summary of product characteristics (SPC) and that the claims made were not supported by clinical evidence. In particular the claim 'Significantly more comfortable than Cosopt' was exaggerated and did not reflect the evidence and the over-emphasis of 'comfort' or 'comfortable', by the inclusion of 13 claims for this in just 8 pages of material, was exaggerated, all-embracing and misleading.

Merck Sharp & Dohme submitted that the data comparing the ocular discomfort of Azarga and Cosopt was not consistent with a general claim that Azarga was 'Significantly more comfortable than Cosopt Solution'. By failing to note in the leavepiece that the cited studies (Vold *et al* 2008; Mundorf *et al* 2008) had measured transient post-instillation discomfort, Alcon misleadingly implied that the discomfort experienced might be longer-lasting and therefore more clinically significant.

Merck Sharp & Dohme stated that the over-emphasis of one aspect of the comparative tolerability, comfort, did not fairly reflect all the evidence. For example the comparisons of comfort between Azarga and Cosopt did not refer to blurred vision which was a common adverse event for Azarga. The Azarga SPC also listed eye irritation and eye pain as common side effects. This was not consistent with describing Azarga as comfortable.

In Vold *et al* patients in both treatment groups (Azarga and Cosopt) reported statistically significant increases in discomfort scores after switching from prior monotherapy to study medicine, and a significant number of patients experienced discomfort on drop instillation with Azarga. The increase in discomfort score for Azarga compared with previous treatment was +0.49, p=0.0028; after 1 week 51% of Azarga patients experienced some discomfort.

There was no definition in the leavepiece of what was meant by comfort. Two studies were described which used different scales and criteria for measuring ocular discomfort but this was also not made clear. Since comfort was not a well-used and understood concept in ophthalmology it appeared all-embracing and misleading when used repeatedly without explanation.

The detailed response from Alcon Laboratories is given below.

The Panel noted that the front page of the leavepiece was headed 'Find comfort in our strength' and featured the claim 'New Azarga Suspension brings you the strength you would expect, with the comfort your patients deserve'. The product logo in the bottom right-hand corner included the strapline 'Where strength meets comfort'. Page 3 of the leavepiece was headed '… and the comfort they desire' and featured a bar chart using data reported in Vold *et al*. The bar chart was headed 'Patients Reported Greater Discomfort with Cosopt than with Azarga Suspension'. A claim above the bar chart read 'Significantly more comfortable than Cosopt Solution'. The bar chart plotted mean ocular discomfort score on a scale from 0 (no discomfort) to 4 (very severe discomfort); at week 1 the mean ocular discomfort score for Azarga (n=48) was 0.77 (1 = mild discomfort) and that for Cosopt (n=47) was 1.53 (2 = moderate discomfort). This difference was statistically significant (p=0.0003). Vold *et al* reported that the distribution of the ocular discomfort scores at week 1 for Azarga was: 0 (no discomfort), 48.9%; 1 (mild discomfort), 34%; 2 (moderate discomfort), 10.6%; 3 (severe discomfort), 4.3% and 4 (very severe discomfort), 2.1%. The comparable distribution of scores for Cosopt was: 0, 14.9%; 1, 38.3%; 2, 27.7%; 3, 17% and 4, 2.1%. The Panel thus considered that although there was a greater likelihood of feeling discomfort following the instillation of Cosopt vs Azarga, 34% of Azarga patients nonetheless reported mild discomfort with Azarga and 17% reported moderate to very severe discomfort. The comparable scores for Cosopt were 14.9% and 46.8%.

The Panel considered that the repeated references to comfort in the leavepiece might be seen as implying that there was no discomfort at all with Azarga which was not so for 24 out of the 47 patients evaluated; one of those patients reported very severe discomfort. The Panel noted that the Azarga SPC stated that eye pain, eye irritation and foreign body sensation in the eyes were common adverse reactions. Ocular discomfort as defined by Vold et al was any of the following: burning, stinging, a feeling heat or warmth, sharp pain or smarting pain. Foreign body sensation was not included in the definition.

The Panel considered that the claim 'Significantly more comfortable than Cosopt Solution' was exaggerated as alleged and did not reflect the evidence and had not been substantiated. Vold

***et al* had evaluated the ocular discomfort of Azarga and Cosopt and the claim should reflect this. Breaches of the Code were ruled. Upon appeal by Alcon, the Appeal Board considered that the claim was not inconsistent with Vold *et al* or the Azarga SPC. The claim headed a bar chart which provided the relevant data from Vold *et al*. The Appeal Board did not consider that the claim was misleading or exaggerated; it was capable of substantiation and no breach was ruled.**

The Panel considered that the repeated use of comfort/comfortable was exaggerated, all embracing and misleading as alleged. A breach of the Code was ruled which was upheld on appeal by Alcon.

The Panel did not consider that the failure to note that Vold *et al* and Mundorf *et al* measured transient post-instillation discomfort misleadingly implied that the discomfort might be longer lasting and therefore more clinically significant as alleged. No breach of the Code was ruled.

The Panel noted that 'comfort' was not defined in the leavepiece. The two studies cited in support of comfort claims (Vold *et al* and Mundorf *et al*) had, in fact, assessed discomfort. As noted above, Vold *et al* had defined discomfort and asked patients to evaluate any such discomfort on a scale of 0 to 4. Mundorf *et al* had not described what was meant by discomfort but had asked patients to complete an ocular discomfort scale (0 (no discomfort) to 9 (substantial discomfort)) approximately one minute after treatment and to complete a preference question. Although noting its ruling above regarding the use of the word 'comfort', the Panel nonetheless considered that it was misleading as alleged not to define the term. The Panel considered that the leavepiece was misleading and exaggerated as alleged. A breach of the Code was ruled. Upon appeal by Alcon, the Appeal Board noted that the intended audience would understand what comfort meant for their glaucoma patients; Alcon had provided comments from ophthalmologists to support its submission. The Appeal Board considered that it was not misleading as alleged not to define 'comfort' in the leavepiece. The Appeal Board considered that the leavepiece was not misleading or exaggerated in this regard. No breach of the Code was ruled.

With regard to blurred vision, the Panel noted that it was a common side-effect with both Azarga and Cosopt. Although inconvenient for the patient, the Panel did not consider that blurred vision was a discomfort factor. In the context of a discussion about the relative discomfort of Azarga and Cosopt, the Panel did not consider that it was misleading not to refer to blurred vision as alleged. No breach of the Code was ruled.

Merck Sharp & Dohme Limited complained about an eight page, A5 leavepiece (ref AZG:SJ:12/08:LHC) for Azarga (brinzolamide/timolol eye drops) issued by Alcon Laboratories (UK) Limited. Azarga was indicated for the decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma (OAG) or ocular hypertension for whom monotherapy provided insufficient IOP reduction. Merck Sharp & Dohme marketed Cosopt, a dorzolamide/timolol combination with a similar indication. Dorzolamide and brinzolamide were carbonic anhydrase II inhibitors; timolol was a non-selective ß-adrenergic blocker.

COMPLAINT

Merck Sharp & Dohme alleged that the leavepiece, entitled 'Find comfort in our strength', was not consistent with the Azarga summary of product characteristics (SPC) and that the claims made were not supported by clinical evidence. Specifically:

- the claim 'Significantly more comfortable than Cosopt' was exaggerated and did not reflect the evidence and
- the over-emphasis of 'comfort' or 'comfortable', by the inclusion of 13 claims for this in just eight pages of material, was not consistent with the SPC and constituted an exaggerated, all-embracing and misleading claim.

Merck Sharp & Dohme submitted that there was data comparing the ocular discomfort and drop instillation of Azarga and Cosopt which was not consistent with a general claim that Azarga was 'Significantly more comfortable than Cosopt Solution'. The discomfort experienced by patients following instillation of eye drops was transient, lasting a few seconds. The results from the studies referenced in the Azarga leavepiece were based on questions asked immediately after instillation, one of them referred to a period of one minute (Vold *et al* 2008; Mundorf *et al* 2008). Alcon's promotion failed to make clear that the effects referred to were short-lived. By failing to point out that both these studies had measured transient post-instillation discomfort, Alcon misleadingly implied that the discomfort experienced might be longer-lasting and therefore more clinically significant.

Merck Sharp & Dohme stated that there was also an over-emphasis in promotion of one aspect of the comparative tolerability of the two products – comfort as defined by Alcon – which did not fairly reflect all the evidence such that a recipient could form their own opinion of the therapeutic value of the medicine. For example the comparisons of comfort between Azarga and Cosopt did not refer to blurred vision which was a common adverse event for Azarga on drop instillation that could be very distressing for patients. The Azarga SPC also listed eye irritation and eye pain as common side effects. This was not consistent with describing Azarga as comfortable.

In Vold *et al* patients in both treatment groups (Azarga and Cosopt) reported statistically significant increases in discomfort scores after switching from prior monotherapy to study medicine, and a

significant number of patients experienced discomfort on drop instillation with Azarga. The increase in discomfort score for Azarga compared with previous treatment was +0.49, p=0.0028; after 1 week 51% of Azarga patients experienced some discomfort.

There was no definition in the leavepiece of what was meant by comfort. Two studies were described which used different scales and criteria for measuring ocular discomfort but this was also not made clear. Since comfort was not a well-used and understood concept in ophthalmology it appeared all-embracing and misleading when used repeatedly without explanation.

Merck Sharp & Dohme alleged that the Azarga leavepiece was in breach of Clauses 7.2, 7.4 and 7.10.

RESPONSE

Alcon explained that open angle glaucoma (OAG) was a chronic, progressive condition with characteristic changes to the optic disc which, if left untreated, would lead to irreversible blindness. In most OAG patients, lowering of (IOP) (initially with eye drops in most cases) was the only treatment that delayed or halted the progression of the disease. Patients who did not show the characteristic changes to the optic disc, but nevertheless had a higher than normal IOP (ocular hypertension), might also be given similar treatment, as a protective measure.

As OAG was a progressive condition, it required long-term medical treatment which produced little discernible benefit for the patient, since they would not notice any improvement in their vision. For this reason, and because administration of eye drops could be difficult and unpleasant, compliance with therapy might be poor. Failure to comply adequately with treatment would result in an uncontrolled IOP and further loss of vision. One way to encourage good compliance was to reduce the number of eye drops used and so combination therapies, such as Azarga and Cosopt, had been introduced and were becoming increasingly popular.

The pH of tears was close to neutral (pH 7), and although the eye could tolerate a range of pH values around the normal physiological level, the general aim was to produce eye drops with a pH value as close to neutral as possible, in order to provide maximal compatibility with the ocular environment.

Cosopt was introduced first as a slightly acidic solution (pH around 5.6), and as a consequence of the results obtained in clinical trials, the SPC listed burning and stinging as very common side effects. In order to reduce the potential for similar levels of ocular irritation Azarga was formulated as a suspension with a pH of 7.2 and, based on the results from clinical studies, the SPC listed irritation and pain only as common ocular side effects. The Azarga SPC also stated that ocular discomfort upon instillation was significantly lower than for Cosopt. The relatively poor ocular comfort of Cosopt had been confirmed in specifically designed comfort studies and in comparative clinical studies against Azarga and other glaucoma products.

The claim in the leavepiece 'Significantly more comfortable than Cosopt' was the conclusion of a parallel group, randomised ocular comfort clinical study in patients with OAG or ocular hypertension (n=96), (Vold *et al*). Discomfort (defined as feelings of burning, stinging, a feeling of heat or warmth, sharp pain or smarting pain) was assessed on a 5-point scale at baseline for the current glaucoma medicine and then after one week of treatment with either Cosopt or Azarga. Significantly more patients in the Cosopt group reported mild, moderate, or severe ocular discomfort and significantly more patients in the Azarga group reported no ocular discomfort.

Similarly Mundorf *et al*, in a prospective, double-blind, randomized, single-dose, crossover patient preference study involving 127 subjects with ocular hypertension or OAG, reported that mean discomfort scores were significantly lower for Azarga than for Cosopt and that significantly more patients reported eye irritation and eye pain as adverse events after instillation of Cosopt . Manni *et al* (2008), in a one-year, randomized, double-blind, active-controlled, parallel group trial involving 437 patients with OAG or ocular hypertension who required a change in therapy, reported a significantly higher incidence of adverse drug reactions in the Cosopt group primarily due to the higher incidence of ocular irritation (burning) and ocular pain (stinging).

Further, the legitimacy of Alcon's claims must be judged in light of relevant contextual factors. There were currently only two topical fixed dose combination products containing a carbonic anhydrase inhibitor, Azarga and Cosopt. Since Cosopt was launched first and was now well established and familiar to the Azarga leavepiece target audience, it was natural that claims for Azarga should focus on comparative efficacy and safety against Cosopt. Comparative clinical studies, submitted in support of the Azarga marketing authorization application demonstrated no significant difference in efficacy between the products, but a difference in safety, represented by a significantly higher level of reports of eye irritation (ie discomfort) with Cosopt. No significant difference was found in the incidence of other side effects, including blurred vision. As a result, ocular comfort of the two products was directly compared by Vold *et al* and in a patient preference study (Mundorf *et al*). Based on the clinical data and the approved SPC for Azarga, it could therefore be correctly claimed that Azarga was as effective as Cosopt (strength) and exhibited less discomfort (ie was more comfortable). Alcon noted that 'comfort' was only mentioned six times in the leavepiece, without a link to efficacy (strength) also being

made. Alcon did not consider that this was excessive given that comfort was the main differentiator between Azarga and Cosopt.

The leavepiece included claims about efficacy, convenience and comfort. Since comfort was the only significant difference found in clinical studies between Azarga and Cosopt it was reasonable and appropriate that this property was specified by Alcon in communications with ophthalmologists, even if this might be inconvenient to Merck Sharp & Dohme.

Merck Sharp & Dohme's assertion that, 'two studies were described which used different scales and criteria for measuring ocular discomfort but this was also not made clear', was irrelevant considering that the two studies were consistent in using a similar numerical discomfort scale to measure comfort and the patient experience in the two studies clearly was similar – Vold *et al* defined ocular discomfort as any of the following: burning, stinging, a feeling of heat or warmth, sharp pain or smarting pain; Mundorf *et al* reported ocular irritation (burning) and ocular pain (stinging) much more frequently as adverse events with treatment. Alcon submitted that blurred vision was irrelevant to the claims made in the leavepiece as this was not generally considered to be a comfort/discomfort factor (as explained by reference to the statements of eminent practising UK ophthalmologists discussed below). Indeed, in the literature relating to the instillation of eye drops, comfort/discomfort was generally related to subjective symptoms such as burning, stinging and irritation. Blurred vision was not a typical or even common component of any definition of a measure of comfort or discomfort. This was illustrated by references which provided a summary of some recent relevant published papers relating to the treatment of OAG and ocular hypertension (ie the field of expertise of the target recipients of the leavepiece in question).

Further, Mundorf *et al* reported blurred vision separately as an adverse event and distinguished it from discomfort factors. This was an appropriate distinction to make because although more patients experienced blurred vision with Azarga compared with Cosopt, most still preferred Azarga, 'suggesting that the blurred vision occurring with [Azarga] was less annoying than the ocular discomfort experienced with [Cosopt]'. Thus, although Merck Sharp & Dohme evidently found it inconvenient that Azarga had a better comfort profile compared with Cosopt, this was no basis for alleging that the comparison Alcon drew between the two products was unsubstantiated, misleading or not of clinical relevance.

Alcon provided correspondence from ophthalmologists who were highly experienced in treating patients with OAG/ocular hypertension; Alcon noted that they viewed blurred vision and comfort as two distinct issues:

Alcon considered that the information, claims and comparisons regarding the comfort of Azarga complied with the Code, in particular because they were:

> based on an up-to-date evaluation of all the evidence, reflected that evidence clearly and were not misleading (in accordance with Clause 7.2);
>
> the material was sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of Azarga (in accordance with Clause 7.2);
>
> the information, claims and comparisons were substantiated (in accordance with Clause 7.4); and
>
> the claims made were not exaggerated or all-embracing (in accordance with Clause 7.10).

Alcon's compliance with the Code was demonstrated in the discussion below, which addressed the comfort claims in the context of the fundamental issue at stake, namely whether comparative studies measuring 'discomfort' were indicative of a product's 'comfort' profile. Alcon was firmly of the view that they were, based on:

> the use of the words 'comfort' and 'discomfort' and their inter-changeability (ie less discomfort equated to more comfort) in literature relating to ophthalmic products;
>
> ophthalmologists' understanding of the terms;
>
> the nature of the products in question; and
>
> as a matter of natural language.

Alcon submitted that contrary to Merck Sharp & Dohme's disingenuous assertion that comfort was 'not a well-used and understood concept in ophthalmology', the comfort of anti-glaucoma eye drops had frequently been studied. Typically, comfort would be assessed by the measurement or reporting of symptoms of discomfort as in Vold *et al* and Mundorf *et al*. Further, it might be seen from the relevant publications that less discomfort and more comfort were essentially interchangeable concepts. For example, although Mundorf *et al* measured discomfort factors, the authors clearly considered these factors to be indicative of the products' comfort profile:

> 'In the present study, significantly more patients reported blurred vision after instilling [Azarga] compared with [Cosopt]. Despite these observations, most patients in this study still preferred [Azarga], suggesting that the blurred vision occurring with [Azarga] was less annoying than the **ocular discomfort** experienced with [Cosopt].
>
> One important reason for their preference was **ocular comfort**. The patients in our study

reported significantly **lower ocular discomfort** scores after instilling [Cosopt] compared to [Azarga] … **Ocular comfort** is a quality that glaucoma patients desire in an IOP-lowering medication' (emphasis added).

Similarly, in Vold *et al*, comfort and discomfort were both used as shown in the following three example extracts; the publication clearly considered discomfort factors to be indicative of the products' comfort profile (which was why the study was entitled 'A One-Week **Comfort** Study …': (emphasis added)

'The results of this clinical trial demonstrate that the **ocular comfort** of [Azarga] ophthalmic suspension dosed twice-daily **is superior** to that of [Cosopt] dosed twice-daily in patients with open-angle glaucoma or ocular hypertension'.

'Several studies have suggested that **greater comfort** can have a positive effect on patient adherence to IOP-lowering medications'.

'In summary, patients with open-angle glaucoma or ocular hypertension reported **less discomfort** with [Azarga] ophthalmic suspension than with [Cosopt] ophthalmic solution' (emphasis added).

The above example extracts clearly illustrated that comparative studies measuring discomfort factors were indicative of the products' comfort profile. In support of its position Alcon cited publications where greater comfort and less discomfort were interchangeable. Accordingly, the use of the word comfort was not all-embracing in breach of Clause 7.10, or misleading (by exaggeration or otherwise) in breach of Clause 7.2 as alleged. Further, since comfort was the only significant difference found in clinical studies between Azarga and Cosopt, it was reasonable and appropriate that Alcon referred to this property in its communications with ophthalmologists; however, Alcon refuted the suggestion that comfort was over-emphasised.

Alcon submitted that comfort and comfortable were well understood clinical terms used frequently ophthalmologists in their everyday clinical practice including with their OAG/ocular hypertensive patients (to ensure they understood why they had to adhere to therapy). Indeed, at an Alcon advisory panel meeting, the six eminent practising UK ophthalmologists commented that Merck Sharp & Dohme's claims (ie that the data did not support Alcon's claim that Azarga was significantly more comfortable than Cosopt; the word comfort was not well-understood in ophthalmology; and blurring of vision should be reported as an aspect of the comfort of Azarga rather than as a side effect) were not sustainable.

Alcon referred to correspondence from ophthalmologists, experienced in treating patients with OAP/ocular hypertension, which supported its position that the target audience would understand the concept of comfort and comfortable and that the terms, as applied to eye drops for the treatment of patients with OAG or ocular hypertension, were to an extent relative rather than absolute.

Alcon submitted that, the fact that, in Vold *et al*, there was an increase in mean discomfort score when patients were switched from their previous IOP-lowering monotherapy to the fixed combination (brinzolamide/timolol or dorzolamide/timolol) did not mean that the term comfort could not be applied to Azarga, as argued. The comparison drawn was between the respective comfort profiles of the two fixed combination products, compared to one another. It was clear in Vold *et al* that there was a lower increase in mean discomfort score in patients switched to Azarga than in those switched to Cosopt.

Further, although the Azarga SPC listed eye pain and eye irritation (which would both be described as discomfort factors) as common side effects, it was nevertheless legitimate to compare the relative comfort of Azarga and Cosopt. Indeed, the Cosopt SPC listed burning and stinging (which would also be described as discomfort factors) as very common side effects. This distinction was borne out by Vold et al and Mundorf et al which demonstrated greater comfort/less discomfort with Azarga compared with Cosopt; the Azarga SPC which stated that 'in three controlled clinical trials, the ocular discomfort upon instillation of Azarga was significantly lower than that of [Cosopt] and the Azarga European Public Assessment Report (EPAR) which reported that 'The ocular discomfort adverse event related reactions in [pivotal safety and efficacy studies] support the claim of better tolerability of Azarga as compared to Cosopt' and that '… the applicant has justified the claim of overall better tolerability for Azarga compared to Cosopt'.

As acknowledged by Merck Sharp & Dohme there was data which specifically compared ocular discomfort on drop instillation with Azarga and Cosopt. However, according to Merck Sharp & Dohme, such data were not indicative of the comfort profile of Azarga vs Cosopt: 'this [ie, the comparative data] **was not consistent** with a general claim that Azarga was significantly more comfortable than Cosopt' (emphasis added). However, Merck Sharp & Dohme offered no satisfactory explanation as to why it considered that less discomfort upon instillation was inconsistent with more comfort. Indeed, in an apparent attempt to support its assertion that less discomfort was inconsistent with more comfort, Merck Sharp & Dohme stated: 'The discomfort experienced by patients following instillation of eye drops was transient …. By failing to point out that both these studies [Vold *et al* and Mundorf *et al*] had measured transient post-instillation discomfort, Alcon misleadingly implied that the discomfort experienced might be longer-lasting and therefore more clinically significant'.

However, the above statement was totally irrelevant to Merck Sharp & Dohme's point; the fact that the discomfort was temporary did not contradict or undermine the legitimacy of the claim that Azarga was 'Significantly more comfortable than Cosopt', the relevant point being whether the comparative studies measuring discomfort factors were indicative of the products' comfort profile (such that the greater discomfort associated with Cosopt might be translated as the greater comfort associated with Azarga), which they clearly were. The claim did not imply that discomfort was long-lasting or of greater clinical significance than it actually was: indeed, notwithstanding the fact that the discomfort was temporary, Mundorf *et al* stated that 'Patients with ocular hypertension or open-angle glaucoma preferred [Azarga] over [Cosopt]. This is likely due to the greater ocular discomfort associated with [Cosopt]'.

Further, it was evident that greater discomfort – albeit temporary upon instillation – might have a negative effect on patient compliance. Mundorf *et al* stated that: '… it is not unreasonable to believe that patients may take a medication less frequently than prescribed if it is associated with significant side effects, including ocular discomfort'. Similarly, Vold *et al* stated that: 'Several studies have suggested that greater comfort can have a positive effect on patient adherence to IOP-lowering medications'.

Finally, as a matter of natural language it was clear that comfort and discomfort were two sides of the same coin and that more comfortable was synonymous with less uncomfortable (or less discomfort) (in other words, a question of perspective: glass half empty/glass half full was the same thing). In this case, experts in the field used the terminology interchangeably. Alcon provided a comment from a consultant ophthalmologist to support its position in this regard.

Based on the above, Alcon firmly considered that comparative studies measuring discomfort factors were indicative of a product's comfort profile, such that the greater discomfort associated with Cosopt might be translated as the greater comfort associated with Azarga. In this context Alcon noted that in assessing a product's comfort profile, it was logical to measure factors of discomfort rather than comfort, as discomfort was associated with definable signals (such as burning, stinging and pain), the fewer of which there were, the greater the comfort. Further, the means of assessing comfort/discomfort had now been approved by three ethics committees, assessed by the European Medicines Evaluation Agency on two different occasions during two different licence applications and presented in three different peer-reviewed articles, which was further evidence of the robustness of the comparative data for Azarga vs Cosopt and the legitimacy of assessing comfort by reference to factors of discomfort. Therefore, it was natural that the studies under discussion measured factors of discomfort rather than factors of comfort and it did not mean that Alcon should be limited to referring to discomfort instead of comfort.

Accordingly, Alcon believed that the Azarga leavepiece complied with the Code.

The claims and comparisons were based on an up-to-date evaluation of all the evidence. The claim, 'Significantly more comfortable than Cosopt' was based on Vold *et al*. Mundorf *et al* and Manni *et al* provided further support for the comfort claims. The claims and comparisons reflected that evidence clearly because comparative clinical studies measuring discomfort factors were indicative of a product's comfort profile. They did not mislead by exaggeration or otherwise. It was acceptable to make comfort claims in relation to Azarga considering that comfort and comfortable were well-used and understood concepts in ophthalmology which ophthalmologists used in their everyday practice including with glaucoma patients. Further, ophthalmologists understood that the terms comfort and comfortable, as applied to eye drops for the treatment of OAG or ocular hypertension, were to an extent relative rather than absolute; comfort was not claimed in absolute terms. The leavepiece was consistent with the Azarga SPC and EPAR.

Alcon further submitted that the leavepiece was sufficiently complete to enable recipients to form their own opinion of the therapeutic value of Azarga. The leavepiece was directed at ophthalmic specialists who were familiar with 'comfort' terminology as applied to eye drops for the treatment of OAG/ocular hypertension and would appreciate that comfort was typically defined by measuring/reporting factors of discomfort. Alcon thus denied a breach of Clause 7.2.

Alcon denied a breach of Clause 7.4. The claims and comparisons were capable of substantiation and had been substantiated. Reference was made in particular to Vold *et al*, Mundorf *et al* and Manni *et al*. Clinical studies measuring 'discomfort' factors were indicative of a product's comfort profile.

Alcon submitted that the claims made in the leavepiece were not exaggerated because they were consistent with the Azarga SPC and EPAR. Further, the claims were supported by robust scientific evidence; clinical studies measuring discomfort factors were indicative of a product's comfort profile. The terms comfort and comfortable were not over-emphasised in the leavepiece: since comfort was the only significant difference found in clinical studies between Azarga and Cosopt, it was reasonable that Alcon should emphasis this property in its communications with ophthalmologists.

The claims made in the leavepiece were not all-embracing because comfort terminology had a specific application in the ophthalmic field and was well-understood by the specialists to whom the leavepiece was directed. Alcon denied a breach of Clause 7.10.

In light of all the arguments raised above, and given the familiarity ophthalmologists had with the concept of comfort in the context of glaucoma medicines, Alcon denied breaches of Clauses 7.2, 7.4 and 7.10.

PANEL RULING

The Panel noted that the front page of the leavepiece was headed 'Find comfort in our strength' and featured the claim 'New Azarga Suspension brings you the strength you would expect, with the comfort your patients deserve'. The product logo in the bottom right-hand corner included the strapline 'Where strength meets comfort'. Page 3 of the leavepiece was headed '… and the comfort they desire' and featured a bar chart using data reported in Vold *et al*. The bar chart was headed 'Patients Reported Greater Discomfort with Cosopt than with Azarga Suspension'. A claim above the bar chart read 'Significantly more comfortable than Cosopt Solution'. The bar chart plotted mean ocular discomfort score on a scale from 0 (no discomfort) to 4 (very severe discomfort) and showed that at week 1 the mean ocular discomfort score for Azarga (n=48) was 0.77 (1 = mild discomfort) and that for Cosopt (n=47) was 1.53 (2 = moderate discomfort). This difference was statistically significant (p=0.0003). Vold et al reported that the distribution of the ocular discomfort scores at week 1 for Azarga was: 0 (no discomfort), 48.9%; 1 (mild discomfort), 34%; 2 (moderate discomfort), 10.6%; 3 (severe discomfort), 4.3% and 4 (very severe discomfort), 2.1%. The comparable distribution of scores for Cosopt was: 0, 14.9%; 1, 38.3%; 2, 27.7%; 3, 17% and 4, 2.1%. The Panel thus considered that although there was a greater likelihood of feeling discomfort following the instillation of Cosopt vs Azarga, 34% of Azarga patients nonetheless reported mild discomfort with Azarga and 17% reported moderate to very severe discomfort. The comparable scores for Cosopt were 14.9% and 46.8%.

The Panel considered that the repeated references to comfort in the leavepiece might be seen as implying that there was no discomfort at all with Azarga which was not so for 24 out of the 47 patients evaluated; one of those patients reported very severe discomfort. The Panel noted that the Azarga SPC stated that eye pain, eye irritation and foreign body sensation in the eyes were common (≥1/100 to <1/10) adverse reactions. Ocular discomfort as defined by Vold *et al* was any of the following: burning, stinging, a feeling heat or warmth, sharp pain or smarting pain. Vold *et al* did not include foreign body sensation in their definition of ocular discomfort.

The Panel considered that the claim 'Significantly more comfortable than Cosopt Solution' was exaggerated as alleged and did not reflect the evidence. Vold *et al* had evaluated the ocular discomfort of Azarga and Cosopt and the claim should reflect this. A breach of Clauses 7.2 and 7.10 was ruled. The claim had not been substantiated. A breach of Clause 7.4 was ruled.

The Panel further considered that the repeated use of comfort/comfortable was exaggerated, all embracing and misleading as alleged. A breach of Clauses 7.2 and 7.10 was ruled.

The Panel did not consider that the failure to note that Vold *et al* and Mundorf *et al* measured transient post-instillation discomfort misleadingly implied that the discomfort might be longer lasting and therefore more clinically significant as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that 'comfort' was not defined in the leavepiece. The two studies cited in support of comfort claims (Vold *et al* and Mundorf *et al*) had, in fact, assessed discomfort. Vold *et al* had defined discomfort as any one of burning, stinging, a feeling of heat or warmth, sharp pain or smarting pain, and asked patients to evaluate any such discomfort on a scale of 0 – 4 (none – very severe). Mundorf *et al* had not described what was meant by discomfort but had asked patients to complete an ocular discomfort scale (0 (no discomfort) to 9 (substantial discomfort)) approximately one minute after treatment and to complete a preference question. Although noting its ruling above regarding the use of the word 'comfort', the Panel nonetheless considered that it was misleading as alleged not to define the term. The Panel considered that the leavepiece was misleading and exaggerated as alleged. A breach of Clauses 7.2 and 7.10 was ruled.

With regard to blurred vision, the Panel noted that it was a common side-effect with both Azarga and Cosopt. Although inconvenient for the patient, the Panel did not consider that blurred vision was a discomfort factor; it was something a patient experienced rather than felt. Thus, in the context of a discussion about the relative discomfort of Azarga and Cosopt, the Panel did not consider that it was misleading not to refer to blurred vision as alleged. No breach of Clause 7.2 was ruled in that regard.

APPEAL BY ALCON

Alcon disagreed with the Panel's ruling and was concerned that the ruling did not refer to the evidence it had submitted in its response. It was difficult to be clear of the exact reasoning behind the conclusions reached. Nevertheless, Alcon submitted that the Panel's ruling was incorrect on all counts based on the relevance and appropriateness of the claims and the available evidence. The Panel's conclusions did not respect the knowledge and experience of the target audience to which the leavepiece was directed and did not recognise Alcon's right to promote legitimate, relevant and demonstrable differences between Azarga and the brand market leader, Cosopt.

Alcon submitted that the main difference between the two eye drops was that of comfort. This difference was confirmed in two studies, specifically designed to assess comparative comfort (Vold *et al*

and Mundorf *et al*). Alcon's definition of comfort/comfortable was in line with its target audience's definition. Ophthalmologists were experienced in treating patients with OAG/ocular hypertension and very familiar with 'comfort' as it applied to eye drops and with the importance that their patients attached to the concept. This was confirmed in the views expressed by a number of ophthalmologists experienced in the field of glaucoma and previously provided by Alcon.

Alcon submitted that as a matter of natural language it was clear that 'comfort' and 'discomfort' were two sides of the same coin and that 'more comfortable' was synonymous with 'less uncomfortable' (or 'less discomfort') ie, a question of perspective: glass half empty/glass half full were the same thing. Experts in the field used the terminology interchangeably. Accordingly, Alcon's use of 'comfort' complied with their understanding and was therefore not all-embracing or misleading by exaggeration or otherwise. Alcon's ability to promote the difference in comfort that had been demonstrated between Cosopt and Azarga was clinically justified and important. If the Panel's decision was upheld, then Alcon submitted that it would not be able to promote this difference in an accurate or reasonable manner.

Alcon noted that the Code applied to the promotion of medicines to members of the health professions and to appropriate administrative staff. Thus Clauses 7.2, 7.4 and 7.10 only applied as they related to the promotion of medicines to the relevant professional target group outlined and that their interpretation was intended to respect the special experience and understanding of this group. Promotional material should be judged for compliance with the Code based on the target audience's ie ophthalmologists' understanding of the matters covered and not from a non specialist's point of view. The leavepiece at issue, was directed to ophthalmologists who treated patients with glaucoma or ocular hypertension. The management and treatment of glaucoma patients was entirely dealt with in the hospital ophthalmic department and since Alcon only employed a specialist hospital sales force, the target audience for the leavepiece was clearly defined.

Alcon submitted that although the Panel's ruling of a breach of Clause 7.2, 7.4 and 7.10 in relation to the claim 'Significantly more comfortable than Cosopt Solution' was preceded by considerable discussion about the data presented in Vold *et al* and about adverse events listed in the SPC for Azarga, there was no suggestion that this had specifically influenced the Panel's conclusions on this point. However, the Panel noted that Vold *et al* had evaluated the ocular discomfort of Azarga and Cosopt and the claim should reflect this. Alcon therefore assumed that this was the primary reason why the Panel considered that this quote was exaggerated, did not reflect the evidence and had not been substantiated. The title of Vold *et al* was 'A One-Week Comfort Study of BID-Dosed Brinzolamide 1%/Timolol 0.5% Ophthalmic Suspension Fixed Combination Compared to BID-Dosed Dorzolamide 2%/Timolol 0.5% Ophthalmic Solution in Patients with Open-Angle Glaucoma or Ocular Hypertension' (emphasis added). The study was published in the Journal of Ocular Pharmacology and Therapeutics, a peer reviewed and respected ophthalmic journal. The stated aim of the study was to evaluate the ocular discomfort of Azarga vs Cosopt in a group of 95 glaucoma or ocular hypertensive patients. Patients had their current glaucoma therapy assessed on a five point discomfort scale and were then switched to either Azarga or Cosopt, twice daily, and then assessed the trial product on the same discomfort scale after one week of dosing. The mean discomfort score for patients treated with Azarga was 0.77, while for Cosopt it was 1.53, (p=0.0003). The authors concluded that, Azarga was associated with a statistically significant less ocular discomfort profile than Cosopt. This claim could hardly be contested as it was reproduced in the Azarga SPC '(in three controlled clinical trials, the ocular discomfort upon instillation of Azarga was significantly lower than that of Cosopt'). Presumably, therefore, the Panel could not have considered the claim 'Significantly less discomfort than Cosopt' to be in breach of Clauses 7.2, 7.4 and 7.10. However 'comfort' and 'discomfort' were interchangeable (ie less discomfort equated to more comfort). There was no logical difference in meaning between this claim and the claim made, 'Significantly more comfortable than Cosopt' for the following reasons:

- Comfort and discomfort were not absolute terms but were subjective and linguistically they were opposites, such that an increase in discomfort must logically and inevitably result in a decrease in comfort. It was therefore not misleading or inaccurate to conclude that if a product was less uncomfortable (less discomfort) than another, it must be more comfortable. It should be recognised that the claim, 'Significantly more comfortable than Cosopt' did not seek to claim or imply that Azarga was a comfortable solution or would never cause discomfort, it was merely an accurate comparative statement supported by all of the available data.

- Although Vold *et al* used a 'discomfort scale' and expressed their results in terms of comparative discomfort, it was clear that the authors also considered this to be a measure of comparative comfort and indeed that comparative comfort was their primary interest:

    - The title of the published paper began, 'A One-Week **Comfort** Study…' (emphasis added)

    - The 'Methods' section stated, 'These parameters and the discomfort scale were the same as those used in a published study comparing the **comfort** of brinzolamide and dorzolamide' (emphasis added).

- The 'Statistical Analysis' section stated 'The primary statistical aim of this study was to demonstrate that the **ocular comfort** of (Azarga) dosed twice daily is superior to that of (Cosopt) dosed twice daily' (emphasis added).

- The 'Discussion' section stated, 'The results of this clinical trial demonstrate that the **ocular comfort** of (Azarga) dosed twice daily is superior to that of (Cosopt) dosed twice daily in patients with open-angle glaucoma or ocular hypertension' (emphasis added).

Alcon submitted that ocular discomfort scales were relatively commonly used in the ophthalmic literature to assess the comparative comfort of ophthalmic products and 'discomfort' and 'comfort' were used interchangeably. Evidence to support this contention, in the form of published references and expert testimony, was provided to the Panel. Therefore the claim, 'More comfortable than Cosopt', accurately reflected Vold *et al*; was consistent with the conclusions and intentions of the authors and would not be considered exaggerated, misleading or unsubstantiated by the target audience for the leavepiece, ie glaucoma specialists.

Alcon submitted that in any event, it should be recognised that in Vold *et al*, the mean discomfort score for subjects receiving Azarga was 0.77 and for Cosopt was 1.53 on a scale ranging from 0 to 4. In other words, both of these products (particularly Azarga) were judged to be far closer to the 'no discomfort' end of the scale than to the 'severe discomfort' end. In a similar study (Mundorf *et al*), the comparative comfort of Azarga and Cosopt was assessed on a 10 point discomfort scale (0= no discomfort to 9= severe discomfort). In this study, the mean discomfort scores were 1.4 and 2.9 for Azarga and Cosopt respectively; again heavily skewed towards the lower 'no discomfort' end of the scale. It was therefore more relevant and more representative to refer to a difference in comfort rather than in discomfort.

Alcon submitted that it was also relevant that no attempt had been made to disguise the nature of and evidence behind the claim 'more comfortable than Cosopt'. In the leavepiece this claim was made immediately above a bar chart that clearly represented 'mean discomfort scores' taken from Vold *et al* and the discomfort scale used was also included.

Alcon submitted that although it was not made clear in its ruling, it suspected that the Panel's consideration of this claim was affected by its general views on the use of the words comfort/comfortable as they applied to Azarga. These views would be considered below. However, regardless of the outcome of the appeal below, this ruling should be considered as an independent matter and that the claim, 'more comfortable that Cosopt', was not exaggerated, was an accurate reflection of the data and had been adequately substantiated. It was therefore not in breach of Clauses 7.2, 7.4 and 7.10.

Alcon noted that the Panel further considered that the repeated use of comfort/comfortable was exaggerated, all embracing and misleading as alleged. A breach of Clauses 7.2 and 7.10 was ruled. Alcon submitted that the justification for this ruling was not made clear. The Panel's ruling not only reflected an unnecessarily negative and inaccurate interpretation of the data presented but also indicated that the Panel might not be sufficiently familiar with glaucoma practice.

Alcon submitted that the Panel chose to characterise the data from Vold *et al* by stating that 17% of patients receiving Azarga reported mild to very severe discomfort. In fact, only 6.4% of patients reported severe or very severe discomfort, while 82.9% of patients reported no or mild discomfort. Almost half of all patients receiving Azarga (48.9%) reported no discomfort. The instillation of eye drops was generally a fairly unpleasant experience. The results obtained by Vold *et al* in patients who had previously been stabilised on other glaucoma medications (in some cases only used once daily rather than twice daily as with Azarga), which they would have been acclimatised to, when switched to a completely new eye drop and then assessed after only one week of use were considered to be excellent and demonstrated that Azarga could be described as a 'comfortable' product. The comparative results for Cosopt also demonstrated that Azarga could be considered by the ophthalmologists to be 'comfortable' when compared to the market leader in this sub-sector. The fact that the mean discomfort score for both test products was significantly higher than the baseline score did not indicate that Azarga could be considered to be 'uncomfortable', since the results were not truly comparable. The baseline figure represented the score given by the patient for an established therapy, which they had become used to, possibly over a long period of time, while the score for the test products represented a score given to a new 'trial' product. To obtain a fair comparison, an evaluation of the initial therapy should have been made in a double-masked fashion after a washout period. However, the comparison between the scores obtained with Cosopt and Azarga was valid.

Alcon submitted that the Panel also seemed to have considered that the listing of eye pain, eye irritation and foreign body sensation in the Azarga SPC had particular relevance to the use of the words comfort/comfortable. This represented a distortion of the situation with glaucoma therapy. The SPCs of eye drops commonly used in glaucoma, where incidence of adverse events was included in the SPC, all listed symptoms of discomfort as common or very common adverse effects. Indeed, the SPCs of artificial tear preparations, products designed specifically to improve the comfort of dry eyes, found similar results, although, due to lack of controlled clinical studies with some older products,

details on the incidence of the side effects were sometimes not available. Alcon submitted the reported incidence of comfort related side effects listed in the SPCs of a number of glaucoma products and artificial tears (as defined by Vold *et al*).

Alcon submitted that in the two large long-term studies referenced in the leavepiece (Manni *et al* and Kaback *et al* (2008)) the reported incidence of these three adverse effects (eye pain, eye irritation and foreign body sensation) was towards the low end of the range defined by the term 'Common side effects' as shown in the table below.

Study	Product	Eye pain	Eye irritation	Foreign body sensation
Manni *et al* (n=220)	Azarga	2.7%	2.7%	1.4%
	Cosopt	6.5%	10.6%	0.5%
Kaback *et al* (n=174)	Azarga	1.1%	2.9%	0.6%
	Timolol	1.1%	3.4%	0.6%

Alcon submitted that these figures clearly indicated the comparatively low level of such complaints reported with Azarga. The comparison with the results obtained with timolol in Kaback *et al* were particularly revealing, since timolol had for a long time, been the treatment of first choice for many glaucoma patients and represented the standard against which other treatments were generally judged.

Alcon submitted that it was therefore unreasonable for the Panel to suggest that Azarga could not be classified as 'comfortable' compared with Cosopt based on the comments that it had made in its review of the data. Comfort and discomfort were subjective, relative terms that were commonly used in ophthalmology and were well understood by the glaucoma specialist who routinely dealt with patients using eye drops on a long-term basis. Expert testimony to this effect had been provided to the Panel. The Panel was therefore wrong to suggest that the repeated references to comfort in the leavepiece might be seen as implying that there was no discomfort at all with Azarga. This suggestion was inaccurate and could not be justified in relation to the target audience and took inadequate account of their knowledge and experience.

Alcon submitted that within the field of glaucoma therapy, the available data was consistent with the description of Azarga as a comfortable solution. The repeated use of comfort/comfortable in the leavepiece was not in breach of Clauses 7.2 and 7.10.

Alcon noted that the Panel had considered it misleading not to define the term 'comfort' in breach of Clauses 7.2 and 7.10. Alcon submitted that 'comfort' was commonly used by ophthalmologists working with glaucoma patients and was well understood. This was illustrated by expert testimony provided to the Panel and was also evidenced by the fact that it was often considered that 'comfort' and 'discomfort' did not need to be defined in the ophthalmic literature. An example of this was provided by Mundorf *et al* as quoted by the Panel, but other examples were provided in Alcon's response above. It was therefore not necessary to define 'comfort' in a leavepiece directed solely to this target audience. Under these circumstances, failure to define the term was not in breach of Clauses 7.2 and 7.10.

In summary, Alcon submitted that this case should not have come before the Panel if Merck Sharp & Dohme had accepted the target audience's and patients' definition of comfort as intended within the leavepiece.

COMMENTS FROM MERCK SHARP & DOHME

Merck Sharp & Dohme stated that Alcon did not appear to have used any substantive additional arguments to support its appeal.

In relation to the claim 'Significantly more comfortable than Cosopt Solution' Merck Sharp & Dohme noted that Alcon had repeated its assertion that Vold *et al* showed a significant difference in favour of Azarga but continued to ignore that the report showed the majority of Azarga study subjects reported discomfort. Considerations such as the use of the word comfort in the study's title, in the Methods, Statistical Analysis and Discussion sections of the report, and its interchangeability or otherwise with discomfort made no difference to Merck Sharp & Dohme's allegation that a claim for superior ocular comfort was misleading on the basis of the supporting scientific evidence.

Merck Sharp & Dohme continued to allege that a claim for Azarga, a product producing significant levels of discomfort in most patients, being more comfortable than a competitor was misleading. It was regrettable that many of the active constituents in topical glaucoma treatments caused post-instillation discomfort, if this affected only a minority of patients 'more comfort' claims might be acceptable. While the situation remained as it was Merck Sharp & Dohme disagreed with Alcon's contention that 'more comfort' and 'less discomfort' should be interchangeable. Merck Sharp & Dohme therefore agreed with the Panel that there had been breaches of Clauses 7.2, 7.4 and 7.10.

Merck Sharp & Dohme noted that in relation to the repeated use of comfort/comfortable, Alcon had repeated its previous arguments in support of its comfort claim. In doing so it had overlooked the implication in the leavepiece that a product causing significant discomfort in the majority of patients was comfortable. This implication had been achieved by the repeated use of 'comfort' or 'comfortable'. Such overuse of this phraseology in this context constituted a misleading claim that was also exaggerated or all-embracing. Merck Sharp & Dohme therefore agreed with the Panel that there had been breaches of Clauses 7.2 and 7.10.

Merck Sharp & Dohme alleged that the use of claims based on comfort or comfortable in this context, relying on scientific data such as that presented by Vold et al or Mundorf *et al*, was misleading if no attempt was made to define the terminology used. Once again Alcon had relied on verbatim comments from selected experts to support its contention that comfort was a widely-understood concept in this therapy area. However, ophthalmologists used a variety of topical products to treat numerous other conditions besides glaucoma. An assumption that a prescriber would immediately appreciate the specific post-instillation discomfort issues when viewing the Azarga leavepiece and use this knowledge in interpreting the data appropriately without adequate further explanation was unfounded. Merck Sharp & Dohme therefore agreed with the Panel that there had been breaches of Clauses 7.2 and 7.10.

APPEAL BOARD RULING

The Appeal Board noted that page 3 of the leavepiece featured a bar chart using data from Vold *et al*. The bar chart was headed 'Patients Reported Greater Discomfort with Cosopt than with Azarga Suspension'. The claim at issue 'Significantly more comfortable than Cosopt Solution' appeared above the bar chart. The bar chart plotted mean ocular discomfort score on a scale from 0 (no discomfort) to 4 (very severe discomfort) and showed that at week 1 the mean ocular discomfort score for Azarga (n=48) was 0.77 (1 = mild discomfort) and that for Cosopt (n=47) was 1.53 (2 = moderate discomfort). This difference was statistically significant (p=0.0003). Vold *et al* reported that the distribution of the ocular discomfort scores at week 1 for Azarga was: 0 (no discomfort), 48.9%; 1 (mild discomfort), 34%; 2 (moderate discomfort), 10.6%; 3 (severe discomfort), 4.3% and 4 (very severe discomfort), 2.1%. The comparable distribution of scores for Cosopt was: 0, 14.9%; 1, 38.3%; 2, 27.7%; 3, 17% and 4, 2.1%.

The Appeal Board noted that Vold *et al* (a peer reviewed study) aimed to evaluate ocular discomfort and concluded that Azarga was associated with a statistically significantly less ocular discomfort profile than Cosopt. Although the authors evaluated ocular discomfort the title of Vold *et al* was 'A One-Week Comfort Study …'. In the statistical analysis section Vold *et al* stated that 'The primary statistical aim of this study was to demonstrate that the ocular comfort of [Azarga] dosed twice-daily is superior to that of [Cosopt] dosed twice-daily'. Similarly the discussion section stated that 'The results of this clinical trial demonstrate that the ocular comfort of [Azarga] dosed twice-daily is superior to that of [Cosopt] dosed twice-daily in patients with open-angle glaucoma or ocular hypertension'. It appeared that Vold *et al* had used 'comfort' and 'discomfort' interchangeably.

The Appeal Board noted that the Azarga SPC stated that 'In three controlled clinical trials, the ocular discomfort upon instillation of Azarga was significantly lower than that of [Cosopt]'. Vold *et al* was one of the three studies referred to (the others being Manni *et al* and Mundorf *et al*).
The Appeal Board considered that the claim that Azarga was 'Significantly more comfortable than Cosopt Solution' was not inconsistent with Vold *et al* or the Azarga SPC. The claim headed a bar chart which provided the relevant data from Vold *et al*. The Appeal Board did not consider that the claim was misleading or exaggerated; it was capable of substantiation. The Appeal Board therefore ruled no breach of Clauses 7.2, 7.4 and 7.10. The appeal on this point was successful.

The Appeal Board noted that other uses of 'comfort' and 'comfortable' were not within the context of a comparison with Cosopt; the terms were used as absolutes. These included the front page of the leavepiece headed 'Find comfort in our strength' which featured the claim 'New Azarga Suspension brings you the strength you would expect, with the comfort your patients deserve'. The product logo in the bottom right-hand corner included the strapline 'Where strength meets comfort'. Page 3 of the leavepiece was headed '… and the comfort they desire'. Pages 4 to 8 also included general claims for 'comfort' per se and/or the product logo and strapline. The Appeal Board considered that the cumulative effect of the repeated references to comfort and/or comfortable, as absolutes, in the leavepiece might be seen as implying that there was no discomfort at all with Azarga which was not so. Many patients with glaucoma were asymptomatic and therefore using eye drops twice a day would not be considered comfortable. Also Vold *et al* reported that with Azarga for 24 out of the 47 patients evaluated one of those patients reported very severe discomfort and over half of all the patients reported some level of discomfort (mild 34%, moderate 10.6%, severe 4.3% and very severe 2.1%). The Appeal Board noted that the Azarga SPC stated that eye pain, eye irritation and foreign body sensation in the eyes were common (≥1/100 to <1/10) adverse reactions. Ocular discomfort as defined by Vold *et al* was any of the following: burning, stinging, a feeling of heat or warmth, sharp pain or smarting pain. Vold *et al* did not include foreign body sensation in their definition of ocular discomfort.

The Appeal Board considered that the repeated use of 'comfort' and/or 'comfortable' was exaggerated, all embracing and misleading as alleged. The Appeal Board upheld the Panel's ruling of a breach of Clauses 7.2 and 7.10. The appeal on this point was unsuccessful.

The Appeal Board noted that 'comfort' was not defined in the leavepiece; the two studies cited in support of comfort claims (Vold *et al* and Mundorf *et al*) had evaluated discomfort. Vold *et al* had defined discomfort as any one of burning, stinging, a feeling of heat or warmth, sharp pain or smarting pain, and asked patients to evaluate any such

discomfort on a scale of 0 – 4 (none – very severe). Mundorf *et al* had not described what was meant by discomfort but had asked patients to complete an ocular discomfort scale (0 (no discomfort) to 9 (substantial discomfort)) approximately one minute after treatment and to complete a preference question. The Appeal Board noted that the Azarga SPC had not defined discomfort in the statement 'In three controlled clinical trials, the ocular discomfort upon instillation of Azarga was significantly lower than that of [Cosopt]'.. The Appeal Board noted that the third clinical trial referred to, Manni *et al* was, unlike the other two (Vold *et al* and Mundorf *et al*), a safety and efficacy trial comparing Azarga and Cosopt. In Manni *et al* the only adverse event that occurred with a statistically significantly different frequency between the two treatment groups and that contributed to the meaning of discomfort was ocular irritation; six patients in the Azarga group (n=220) reported eye irritation vs twenty three in the Cosopt group (n=217), p=0.0009.

The Appeal Board noted that the intended audience was an important consideration. In this instance ophthalmologists would understand what comfort meant for their glaucoma patients; Alcon had provided comments from ophthalmologists to support its submission. The Appeal Board considered that it was not misleading as alleged not to define 'comfort' in the leavepiece. The Appeal Board considered that the leavepiece was not misleading or exaggerated in this regard. No breach of Clauses 7.2 and 7.10 were ruled. The appeal on this point was successful.

Complaint received **17 December 2009**

Case completed **12 May 2010**

CASE AUTH/2290/12/09

ANONYMOUS CLINICIAN v ASTELLAS PHARMA

Mycamine advisory board

An anonymous and uncontactable 'concerned' hospital clinician complained on behalf of himself and his colleagues about a Mycamine (micafungin) advisory board conducted by Astellas Pharma.

The complainant noted that he was invited to a series of advisory boards in June/July 2009 which he believed were held all over the country. He attended one of these meetings in good faith. The complainant had no particular issue with the agenda on the day but got the feeling that he was being promoted to, more than having his advice sought. It was not entirely fair to say that the whole advisory board was promotional though he thought it had too many presentations.

The complainant noted that after the meeting a member of the Astellas team visited him. The complainant glimpsed a document with his name on it and those of a few other clinicians who had attended the meeting. He insisted on viewing it. Much to his distaste, there was clear detailing of various attendees and what they thought about Mycamine. It further analysed and detailed who should be promoted to and whose opinion had been changed by the advisory board with regard to prescribing Mycamine. The complainant wondered whether the entire point of the advisory board was to promote Mycamine.

The Astellas employee refused to give the complainant a copy of the document. He was taken into 'confidence' and pleaded with not to take this further. The employee told the complainant that Astellas had asked an agency to draw up the document but there had been an issue at the Astellas head office. The employee had stated that a medical manager had lost her job because she had not wanted the document to be distributed but the medical director had agreed to the document being distributed and so the employee did not feel that he was doing anything wrong. The complainant was shocked at the unethical behaviour of the company and he and his colleagues were annoyed that such information about consultants was compiled and distributed. They attended advisory boards to give an expert opinion with the hope that the information was used in a productive manner, not to have detailed profiles on themselves drawn up and distributed. Furthermore this advisory board was clearly intended to be promotional as the outcomes from it as noted in the document clearly detailed prescribing inclination before and after the advisory board.

The detailed submission from Astellas is given below.

The Panel noted that the advisory board programme consisted of three pairs of regional meetings with each meeting chaired by either by Astellas' previous interim medical director or the current medical director. The plan was for twelve advisors from each region to attend both meetings.

Each meeting began at 8.45am with tea and coffee and finished at 4.30pm. The agenda for the first meeting detailed six presentations of varying length totalling 5 hours; some of the presentations incorporated short group exercises. Round table introductions and feedback were each allocated 30 minutes. The rest of the agenda was taken up with refreshment breaks of 75 minutes. The agenda for the second meeting was similar to that of the first; again, some of the presentations included breakout or group exercises. However from the slides provided it appeared that much of the time at both meetings would be spent on presentations.

The invitation to participate in the advisory boards was signed by a senior brand manager. The letter stated that the company was seeking guidance and support in the future development and marketing of Mycamine; active participation was sought. £1,000 would be paid. The company wanted to understand local issues and work on better management solutions. The letter confirming engagement as an advisory board member stated that the recipient had been approached on the basis of their professional skills, expertise and knowledge of the therapeutic area, specifically candida infections. The letter set out the terms and, *inter alia*, asked participants to agree to the meetings being recorded and that material being used for the company's own business purposes. Participants also consented to use of their details in an internal database for business purpose use.

Advisors were selected for invitation largely on the basis of recommendation from key account managers (KAMs) and in that regard advice to the KAMs from the senior brand manager referred to the potential advisors as 'Mycamine advocates'. The KAMs were told that, *inter alia*, nominees had to have a belief in Mycamine, a sphere of influence including drugs and therapeutics, previous experience in getting drugs onto a formulary and a desire to work with Astellas and become a brand advocate. Brand advocacy was not referred to in the invitation to advisors nor in the letter confirming engagement. The email from the senior brand manager to the KAMs also referred to the importance of maintaining momentum if the

uptake of Mycamine was to be increased through quarter 4 and beyond.

The Panel noted that the purpose of any advisory board meeting was for a company to collect health professionals' views and advice; it was not an opportunity to promote medicines. In that regard the Panel questioned the appropriateness of the advisors being nominated by members of the field force, supervised by the national sales manager. The agenda should allow adequate time for discussion and participation by all. The Panel queried whether that was so. The Code required that there must be a legitimate need for the services and the criteria for selecting consultants must be directly related to the identified need. The hiring of health professionals must not be an inducement to prescribe, supply, administer, recommend, buy or sell any medicine.

The Panel was concerned that Astellas had used the pre-advisory board dinners as an opportunity for its medical and scientific liaison (MSL) staff to build relationships with the health professional attendees. It did not appear that participants were aware that their personal views would be provided to the MSLs and others to enable subsequent relationships to be built. The document setting out the views of participants was headed that the document was for MSL managers and not intended for use by sales representatives given that the content was obtained in an advisory board setting and it was not appropriate to take comments or recommendations and apply them in an alternative context.

MSL managers were advised that they could contact any advisory board member who had informally suggested another meeting or who had given them their business card; they were not to contact anyone who did not know them and when making contact MSLs were to develop relationships to expand their knowledge in the treatment area. MSLs were not to request visits to speak about Mycamine as this would make the visit promotional. Such visits should be carried out separately by the sales force.

The Panel was concerned about the role of the MSLs in that the Code defined a representative as anyone who called upon health professionals and/or administrative staff in relation to the promotion of medicines. Involving the MSLs in the advisory board meetings and follow-up meant that any subsequent discussion was not reactive ie not in response to a specific unsolicited enquiry and thus unable to take the benefit of the exemption to the definition of promotion as set out in the Code.

As part of the follow-up participants were asked by letter to discuss any further points with the KAMs who had been provided with details of the named individual participants' contributions and views relevant to the KAM's geographical area. This material appeared to be similar to that circulated to the MSL managers but without the heading stating, *inter alia*, that the material was not intended for use by sales representatives. Astellas had approved circulation of this material to the representatives and had considered that it did not need certification. A presentation had been prepared for the KAMs' internal use only. This had been certified. A spreadsheet setting out participants' views had also been circulated to the KAMs. Astellas had not approved circulation of this material to the representatives and it had not been certified. The Panel was very concerned at the nature and level of the detail provided to the KAMs. It did not consider that providing such reports to the sales force was consistent with the agreement that transcripts from the meetings could be used for Astellas' internal business purposes. The presentation and spreadsheet detailed feedback ranking ie from 0, limited use of echinocandins (caspofungin only); ignorant of Mycamine to 10, Mycamine on formulary; use of Mycamine; on message; willing to advocate to others. The data showed that compared to baseline the ranking had improved after the first advisory board and further gains had been made following the second meeting. The feedback ranking summary slide was headed 'Raise awareness and create motivation to support/prescribe Mycamine' and stated '93% positive shift of opinion towards Mycamine'. The Panel considered that the data produced as an outcome of the advisory board and shared with the sales force reinforced the impression that the purpose of the advisory board was, at least in part, to change the views of participants regarding Mycamine ie to promote the product rather than just elicit views and advice. The Panel acknowledged that any advisory board on a particular medicine would inevitably have some promotional impact on the participants. In the Panel's view, however, that such impact was evaluated and then communicated to the field force demonstrated an intention to promote Mycamine and positively change participants' views about the product.

The agenda and objectives as described to participants were not necessarily unacceptable. The selection criteria communicated to the KAMs, ie that the company expected advisory board members to *inter alia*, become brand advocates, was not an acceptable outcome for a genuine advisory board. The Panel considered that the provision of detailed information regarding advisory board members' position with regard to their personal use of Mycamine to the MSL managers and the KAMs (who promoted the medicine) was unacceptable as was the failure to certify briefing material for the representatives. The Panel also considered that the roles of the KAMs and MSLs before and after the meetings were inappropriate and inconsistent with the non-promotional purpose of an advisory board. In the Panel's view the overall arrangements for the advisory boards showed that they had, at least in part been held for a promotional purpose and to develop brand advocates/opinion leaders rather than solely for gathering expert advice and opinion.

Thus the Panel ruled that the overall arrangements for the advisory boards were disguised promotion in breach of the Code. The payment of a fee to attend a promotional event was unacceptable and in effect an inducement to prescribe, administer or recommend a medicine. A breach of the Code was ruled.

The Panel considered that, given the overall arrangements for the advisory boards, Astellas had failed to comply with the requirements of relating to consultants. It was not a genuine consultancy arrangement given the discrepancy between internal and external documents and the involvement of the KAMs and MSLs. The Panel was also concerned that the hiring of the health professional might be in effect an inducement to prescribe, administer or recommend Mycamine. A breach of the Code was ruled.

The Panel considered that the overall arrangements had not maintained a high standard and thus a breach of the Code was ruled. With regard to Clause 2, the Panel noted that this was reserved for use as a particular sign of censure. The Panel considered that the overall arrangements, particularly the development of brand advocates under the guise of an advisory board, brought discredit upon and reduced confidence in the pharmaceutical industry and in that regard ruled a breach of the Code.

An anonymous and uncontactable 'concerned' clinician complained about a Mycamine (micafungin) advisory board conducted by Astellas Pharma. The complainant stated that he wrote on behalf of himself and his colleagues. He wished to remain anonymous to protect an Astellas employee and to avoid any further uncomfortable dealings with the company.

COMPLAINT

The complainant noted that he was invited to a series of advisory boards in June/July 2009 which he believed were held all over the country. He attended one of these in good faith, believing that they would be like the many other advisory boards he had attended over the years. The complainant had no particular issue with the agenda on the day but got the feeling that he was being promoted to, more than having his advice sought. It was not entirely fair to say that the whole advisory board was promotional though he thought it had too many presentations.

The complainant noted in particular that after the advisory board a member of the Astellas team visited him at the hospital. The complainant glimpsed a document with his name on it and those of a few other clinicians who had attended the advisory board. He insisted on viewing it. Much to his distaste, there was clear detailing of various attendees and where they were with regard to their opinion of Mycamine. It further analysed and detailed who should be promoted to and whose opinion had been changed by the advisory board with regard to prescribing Mycamine. Given this detailed information on what had ensued in the advisory board, the opinions and perceived status of consultants and their willingness to prescribe and get the medicine on formulary, the complainant wondered whether the entire point of the advisory board was to promote Mycamine.

The complainant asked the Astellas employee for the document as it had detailed information about himself and several of his colleagues. The employee absolutely refused. He was taken into 'confidence' and pleaded with not to take this further. The employee told the complainant that the document had been drawn up by an agency on instruction of Astellas but there had been an issue at the Astellas head office. A medical manager had lost her job because she had shown some resistance to them being distributed. The complainant was further told by the employee that the medical director whom he had met at the advisory board, had said that they were fine to be distributed and used so the employee did not feel that he was doing anything wrong. The complainant was shocked at the unethical behaviour of the company.

The employee was fearful of being sacked. The complainant discussed this issue with his colleagues and they decided that to protect the employee they would complain anonymously. They were, however, absolutely annoyed that information of such a nature on consultants was compiled and distributed. They attended advisory boards to give companies an expert opinion with the hope that the information was used in a productive manner, not to have detailed profiles on themselves drawn up and distributed. Furthermore this advisory board was clearly intended to be promotional as the outcomes from it as detailed in the document clearly showed which consultant had changed his mind about Mycamine after the advisory board. It detailed prescribing inclination before and after the advisory board.

When writing to Astellas, the Authority asked it to respond in relation to Clauses 2, 9.1, 12.1, 18.1 and 20 of the Code.

RESPONSE

Astellas stated that the complainant had referred to an advisory board programme that was held in June and July 2009, and a subsequent conversation between the complainant and an unidentified Astellas employee. The complainant's letter and the allegations therein had been carefully investigated by Astellas.

The advisory boards were planned and conducted as non-promotional activities. As such, the agreements between Astellas and the paid consultant attendees represented business transactions and would thus, together with the meeting content, not normally be subject to the Code. However, in the interests of transparency,

Astellas provided a full account of the programme content and outcome. As indicated in the complainant's letter, an agency had helped Astellas run the meetings.

Following its review Astellas confidently denied any breaches of Clauses 2, 9.1, 12.1, 18 and 20. However, during its investigation Astellas discovered an email sent to the sales team with a document attached that was not approved for distribution. As a consequence Astellas acknowledged that inappropriate material was given to its sales representatives. This action served no apparent purpose and was the result of the unilateral action of one employee, who had subsequently left the company. Astellas acknowledged a breach of Clauses 14 and 15.9, for which it apologised unreservedly.

Astellas submitted that the advisory board programme had a clear purpose. A year after its UK launch in August 2008, Mycamine's adoption in the UK had been significantly below expectation and out of keeping with its overall global commercial performance. Further Astellas was relatively new to the specialist therapy area of anti-infectives in the UK (Mycamine was the only agent that Astellas currently marketed in this therapy area in the UK) and opportunities to gather constructive comment on the product, its attributes and the marketing approach from relevant external sources had been limited. It was, therefore, clearly commercially important to try to calibrate the marketing campaign against the needs and expectations of UK infection specialists and their patients.

The advisory board programme consisted of three pairs of non-promotional meetings, each meeting (of the pair) having separate content. The second meeting essentially built on what was discussed at the first. Meetings were held in Edinburgh, Birmingham and London and each was chaired by senior Astellas medical personnel. The first two meetings were chaired by a senior external consultant who had previously been an interim medical director at Astellas. The remaining meetings were chaired by the current medical director. Astellas medical was closely involved with planning for the meetings and attended the meetings themselves.

The meeting programme comprised a balance of presentations (some by practising clinicians). Case presentations were included to help ensure discussions were clinically focussed and a number of other interactive discussion sessions and small group work featured prominently in the agenda. Overall the programme was specifically designed to stimulate discussion and allow the advisors (or attendees) to contribute their views and opinions.

The phase 1 meetings began with a candid summary of Astellas' position in the anti-infectives market and the adoption of Mycamine. The meeting objectives were clearly laid out in this context.

The agency that helped Astellas run the meetings had run scientific and commercial advisory boards for many years and had developed a format that engaged participants in a manner that enhanced the quality of the meeting outputs. The precise format had been used in meetings by other UK pharmaceutical companies. The programme objectives were agreed by the agency with Astellas in February 2009. The agency staff were highly experienced in this work and well aware of the Code and other regulations governing pharmaceutical company activity in the UK.

The aim was to recruit 12 advisors to participate at each meeting location and the eventual attendance approximated this number. This size of programme (number of meetings and advisors) was not out of keeping with the objectives of the advisory boards and their advisory nature. The meeting objectives included identification of regional differences in views obtained. It was important to ensure that the advice obtained was valid as far as was reasonably possible across the UK.

Advisors were selected for invitation largely on the basis of recommendations from the key account managers (KAMs) for anti-infectives – senior field based employees whose job was to know those involved in local decision making regarding medicines usage. KAMs were highly experienced and well versed in company protocols and procedures, as well as being ABPI trained and certified. The KAMs were given clear and appropriate guidance from the senior product manager in order to recommend advisors. The national sales manager also supervised the recommendation of advisors.

The invitation to potential advisors clearly laid out the meeting objectives and was examined by an Astellas medical advisor in line with the requirements of the Code and Astellas company policy. Advisors were mainly microbiologists but senior laboratory mycologists, senior pharmacists and intensive care physicians also attended. Each advisor had relevant specialist knowledge and insight into clinical care of patients, and their professional standing was respected and valued by Astellas.

Each advisor signed a consultancy agreement with the company prior to the meetings as required under Clause 20.1. The agreement allowed Astellas and its affiliates to use a recording of the meetings for internal business purposes. Microphones and a medical writer from the agency were present.

Advisors received an honorarium of £500 for each of the two advisory boards attended in recognition of the significant time and effort given. In addition accommodation (which was optional and only provided on the evening before the meetings when advisors indicated this was required) and subsistence were provided before and during the meetings. Details were provided. Reasonable travel expenses were also reimbursed.

The objectives of the advisory boards were clearly stated in the invitation sent to the advisors. These were similar and related to the objectives agreed between the agency and Astellas in the Statement of Work dated 24 February 2009. The central purpose was to gather advice on how Astellas could optimise the marketing campaign for Mycamine.

Advisors were asked to fill out questionnaires in order to generate objective feedback on the advisory board programme. Astellas noted that 93.5% of advisors gave 4/5 or 5/5 ratings when asked (immediately after each phase 1 meeting) how well they considered the meeting programme met the outlined objectives. The percentage after the phase 2 meetings was 92.6%. In addition the vast majority of advisors considered that they had been given adequate opportunity to contribute: 96.7% of advisors gave a 4/5 or 5/5 rating in response to a question addressing this point on the evaluation forms after the phase 1 meeting. After the phase 2 meetings the figure was 96.3%.

Following each phase of advisory board meetings, summary and full reports were prepared to document the advice and opinion offered at the meetings. These were commissioned by Astellas in advance of the meetings and a medical writer, who had been introduced appropriately, typed notes during the meeting. After the conclusion of the advisory board programmes, an Astellas senior brand manager also requested two additional reports for which the agency performed a post-hoc analysis which required a further review of audio recordings, identification of individual opinions and provision of the documents which were clearly marked as being for internal information only. The first additional report was a summary of views and advice given to Astellas by each advisor during the meeting. The reports, although clearly for internal company use only, were prefaced with a statement that they were for the use of Astellas medical and scientific liaison (MSL) staff.

MSLs were non-promotional staff, who were managed, trained and briefed by the Astellas medical team to respond to the specific requests of health professionals. Such briefings could include providing information on important clinical issues in the therapy area, where the regional KAMs were not able to do this either because it would be inappropriate or if/when they did not have the depth of knowledge required. MSLs were not incentivised on sales.

In line with their non-promotional role, the principles by which the MSLs could therefore approach advisory board members were carefully proscribed by their medical manager. MSLs attended some pre-advisory board dinners in order to build relationships. They did not attend the meetings themselves.

In addition to these summary sheets, the medical writer was asked to review the audio again to create a spreadsheet that captured individual advisors' views on micafungin as a way of summarising opinions throughout the meeting. Advisors were asked their general views on micafungin during the advisory board meeting and this was considered entirely appropriate. The 'benchmarking' of views performed to generate the supplementary report was performed on subjective review of the entire audio by the medical writer after the conclusion of the programme. The views of each advisor would thus equally have been known to all who attended the advisory board.

With any meeting or discussion, an individual's views might change (positively or negatively) or stay the same. The analysis was subjective and was conducted after reflection on the views given and comments expressed by advisors throughout the meetings. This analysis was not intended for use in a promotional context. The document would assist Astellas in the future when organising speaker meetings since it was normal, and indeed good practice, for companies to know the views of their speakers before asking them to speak.

At an Astellas senior management team meeting the spreadsheet was used to present an analysis showing the generally positive nature of the feedback along with identification of other important learnings from the advisory board programme. Astellas contended that the existence of the documents did not undermine or contradict the established objectives of the advisory board programme, and these supplementary documents were prepared as an afterthought.

The comment and advice given in the meetings was generally seen as extremely encouraging. The feedback to Astellas was therefore of vital importance, given the company's investment in marketing Mycamine in the UK. The comment, advice and support for Astellas and Mycamine had been gathered in a robust and credible manner.

The company also had an understandable desire, when reviewing the feedback from advisors, for the open relationship, dialogue and collaboration with advisors to continue where this was appropriate and when there was mutual consent for this on the part of the company and the advisors.

Astellas was always sensitive to the requirements of the Code and respectful of its advisory board members. Such respectful and ethical conduct was pivotal to success in any therapeutic area.

Any breach of the Code that occurred in company activities following the advisory board programme should be seen as an isolated departure from not only from the requirements of the Code, but also the company's own high standards.

Follow up of advisors

It was agreed that the KAMs would continue to liaise with advisors in an appropriate professional capacity assisted, where appropriate, by the MSLs.

Advisors were therefore invited in a letter (that thanked them for their contribution to the advisory boards) to discuss any further thoughts and advice they had with the KAMs. It was made clear in the letter that the granting of such an appointment with the KAMs would be at their discretion. Thus the desire for follow up of the advisory boards, as well as the intended nature of this follow up (and the potential role of the KAM) was clear and transparent.

In addition, and in agreement with the Astellas medical team, it was agreed that the additional reports provided by the agency could be provided to the KAMs to aid their discussions with advisors outside of the advisory board setting. Comments relating to off-licence indications for Mycamine were blacked out of these reports by the Astellas medical advisor. No effort was made to elicit advice on the off-licence use of Mycamine during advisory boards, but advisors occasionally spontaneously referred to such.

The Astellas medical advisor sent a copy of these reports to the KAMs who operated in the territory in which each respective advisor worked, together with the template of the letter that had been sent to the advisors on 11 September 2009. It was considered appropriate for the KAMS to receive these reports, and the action was considered to be consistent with the terms of consultancy agreement, which allowed Astellas to use the transcripts for internal business purposes.

In a covering email the confidential nature of the reports was made clear to the KAMs. Whether this material sent to the KAMs required certification was discussed at the appropriate levels in the company. On reading the attachments however, it was clear that the nature of the comments was similar to that which KAMs would record on their electronic territory management system and it was noted that they did not mention anything about an individual advisor's intention to prescribe Mycamine. It was decided that certification was not required as the material pertained to feedback from non-promotional meetings and did not constitute a general briefing on the product or how to promote it. The decision to make the material available was consistent with the KAMs' senior role.

The feedback was also presented to the KAMs at in the national sales conference on 16 October 2009. This was in the form of a certified presentation the purpose of which was to: summarise the positive nature of the feedback given by the advisors on Mycamine and its differentiating features; encourage and motivate the KAMs; indicate where the marketing claims for the product were to be amended and the reasons for this and to stimulate discussion to enable the team to move forward in a positive and appropriate manner.

The basis for the complaint

Given that the complainant was anonymous, Astellas had not been able to discuss the matter with its employee referred to by the complainant. However Astellas recognised that the complainant was justifiably upset - something which it very much regretted.

Astellas assumed that the complainant was specifically upset about the spreadsheet showing a post hoc benchmarking of advisors' views before, during and after the advisory boards – one of the additional reports, prepared by the agency at the senior brand manager's request, for internal use only after the meeting.

This was the only document that showed a change in views and perceptions regarding Mycamine, the central issue to the complaint. However, Astellas emphasised that it was not the purpose of the advisory boards to elicit a change in opinion, but entirely an unintended consequence. Any negative feedback from the advisory boards would have been similarly presented on the spreadsheet.

The spreadsheet was for head office use only and was not approved for promotional use. It was identified that the nature of the document could be misinterpreted. Quite deliberately it was not approved for use in the field. Astellas was initially unsure how it was obtained by one of its field-based employees and subsequently used in what the complainant judged to be a promotional context. With much regret Astellas had subsequently discovered that the spreadsheet was released on 20 October 2009 by email in an inappropriate manner, without any substantive briefing accompanying it and without consultation. This was the unilateral action of one employee who 14 days later left Astellas to work for another company, having resigned some time before. The release of this post hoc analysis served no apparent purpose and its release by the individual in question was inexplicable. Astellas was badly let down by the actions of this individual. This spreadsheet might also have coloured the complainant's perception of the 'summary of advice' documents that had been approved by the company for release to the KAMs, and which the complainant also seemed to refer to. It was possible that the complainant was only able to briefly study these documents.

Although the email referred to the sales conference where the advisory boards were discussed with the KAMs, the decision to release the email was not openly discussed at the meeting. The possibility of having additional specific information about advisors was raised in the meeting but the Astellas medical advisor in attendance clearly stated that this was inappropriate and further information beyond what had already been provided would serve no purpose. It was indicated that medical approval for release would not be given. The medical advisor consequently did not expect the document to be released against his advice.

Astellas submitted that there was little it could have done to prevent the actions of the individual who

released the document, given that he could not now be held accountable for his action since he had left the company and the company's medical team had advised specifically against release of the document. The email was not sent to any of Astellas' medical staff, and release of the document was therefore concealed from medical colleagues.

Astellas stated that once the email was discovered, the national sales manager instructed the KAMs to destroy the document and not to use it again. Because this was an email attachment there was no material to recover.

Astellas noted that a medical manager's resignation in October 2009 was unrelated to any issues about the advisory board programme or the outcomes and follow up.

Astellas admitted that the document at issue was released without the necessary approval and that this material was inappropriate. Astellas therefore acknowledged a breach of Clause 14 and 15.9. This action was extremely disappointing and had understandably led to the purpose of the advisory boards being misconstrued. However, in general the reports generated for Astellas were handled appropriately and in a manner consistent with the terms of the consultancy agreement that advisors signed.

Astellas was also disappointed with the report of the alleged behaviour of the Astellas employee referred to by the complainant. Their behaviour, once the document had been discovered by the complainant, seemed to have been a reflex reaction. Their response showed a willingness to damage the company's reputation and that of individuals therein with fabricated allegations in a misguided attempt to preserve their own standing with the complainant and with Astellas. The employee's evasion from responsible action (for example by reporting the meeting with the complainant to their manager) precluded the possibility of the company apologising for any offence caused and addressing any misunderstanding with the complainant in person.

Summary

In summary Astellas stressed the high calibre of the Mycamine advisory board meetings programme. Feedback strongly suggested that the meeting objectives were met and that advisors had enough opportunity to contribute. In addition the detailed reports prepared by the agency showed that advice given was painstakingly gathered and analysed. Finally the outcomes documented in Astellas' response showed that it considered the advice carefully and as a result changed the way that Mycamine was marketed. Astellas therefore denied a breach of Clauses 12, 18 or 20.

The substance to the complaint concerned a misunderstanding about the nature of a report that was meant to be for internal use only and not for use in a promotional context. In that regard Astellas had been badly let down by the ex-employee who released the unauthorised material and by the unidentified representative who responded inappropriately when challenged by the complainant. Astellas acknowledged breaches of Clauses 14 and 15.9 because a post hoc analysis of advice was inappropriately released to the sales team, uncertified. The company apologised sincerely for any offence and misunderstanding caused but stressed the high ethical standards of the company and its compliance with these. Astellas denied any systematic failings in its compliance with the Code and therefore denied any breach of Clauses 2 and 9. Astellas did not consider that the reputation of Astellas should be held in disrepute.

PANEL RULING

The Panel noted that the complainant was anonymous and uncontactable. Complaints were judged on the evidence provided by the parties. In this case the complainant had described a document used by the representatives. Astellas acknowledged that inappropriate material that appeared to meet the complainant's description had been supplied to the representatives albeit without the necessary approval.

The Panel noted that the advisory board programme consisted of three pairs of meetings, held in London, Birmingham and Edinburgh, with each meeting chaired by either an external consultant who had previously been Astellas' interim medical director or the current medical director. The plan was for twelve advisors from each region to attend both meetings.

Each meeting began at 8.45am with tea and coffee and finished at 4.30pm. The agenda for the first meeting detailed six presentations of varying length totalling 5 hours; some of the presentations incorporated short group exercises. Round table introductions and feedback were each allocated 30 minutes. The rest of the agenda was taken up with refreshment breaks of 75 minutes. The agenda for the second meeting was similar to that of the first; again, some of the presentations included breakout or group exercises. However from the slides provided it appeared that much of the time at both meetings would be spent on presentations.

The invitation to participate in the advisory boards was signed by a senior brand manager. The letter stated that the company was seeking guidance and support in the future development and marketing activity for Mycamine; active participation was sought. £1,000 would be paid (£500 per meeting). The company wanted to understand local issues and work on better management solutions. The letter mentioned the need for participants to sign an agreement so that information from Astellas could be shared. The letter confirming engagement as an advisory board member stated that the recipient had been approached on the basis of their

professional skills, expertise and knowledge of the therapeutic area, specifically candida infections. The letter set out the terms and asked participants to agree to the meetings being recorded and the use of that material for the company's own business purposes provided this was not broadcast externally or published without prior written consent. Participants also consented to use of their details in an internal database for business purpose use.

Advisors were selected for invitation largely on the basis of recommendation from the KAMs and in that regard advice to the KAMs from the senior brand manager referred to the potential advisors as 'Mycamine advocates'. In nominating such advocates the KAMs were told that, *inter alia*, nominees had to have a belief in Mycamine, a sphere of influence including drugs and therapeutics, previous experience in getting drugs onto a formulary and a desire to work with Astellas and become a brand advocate. Brand advocacy was not referred to in the invitation to advisors nor in the letter confirming engagement. The email from the senior brand manager to the KAMs also referred to the importance of maintaining momentum if the uptake of Mycamine was to be increased through quarter 4 and beyond. The Panel noted that the in-house advice regarding the advisory boards given to the KAMs had a distinct commercial edge, in contrast to the clinical, professional tone of the letters sent to potential advisors as described above.

The Panel noted that the purpose of any advisory board meeting was for a company to collect health professionals' views and advice; it was not an opportunity for a company to promote medicines. In that regard the Panel questioned the appropriateness of the advisors being nominated by members of the field force, supervised by the national sales manager. The agenda should allow adequate time for discussion and participation by all. The Panel queried whether that was so. Clause 20 of the Code required that there must be a legitimate need for the services and the criteria for selecting consultants must be directly related to the identified need. The hiring of health professionals must not be an inducement to prescribe, supply, administer, recommend, buy or sell any medicine.

The Panel was concerned that Astellas had used the pre-advisory board dinners as an opportunity for its MSL staff to build relationships with the health professional attendees. It did not appear that participants were aware that their personal views would be provided to the MSLs and others to enable subsequent relationships to be built. The document setting out the views of participants was headed that the document was for MSL managers and not intended for use by sales representatives given that the content was obtained in an advisory board setting and it was not appropriate to take comments or recommendations and apply them in an alternative context.

MSL managers were advised that they could contact any advisory member who had informally suggested another meeting or who had given them their business card (email dated 12 August 2009). MSLs were instructed not to contact anyone who did not know them and when making contact MSLs were to develop relationships to expand their knowledge in the treatment area. MSLs were not to request visits to speak about Mycamine as this would make the visit promotional. Such visits should be carried out separately by the sales force.

The Panel was concerned about the role of the MSLs in that the Code defined a representative as anyone who called upon health professionals and/or administrative staff in relation to the promotion of medicines (Clause 1.6). Involving the MSLs in the advisory board meetings and follow-up meant that any subsequent discussion was not reactive ie not in response to a specific unsolicited enquiry and thus unable to take the benefit of the exemption to the definition of promotion as set out in Clause 1.2.

As part of the follow-up participants were asked by letter (9 September) to discuss any further points with the KAMs who had been provided with details of the named individual participants' contributions and views relevant to the KAM's geographical area (email dated 11 September). This material appeared to be similar to that circulated to the MSL managers but without the heading stating, *inter alia*, that the material was not intended for use by sales representatives. Astellas had approved circulation of this material to the representatives and had considered that it did not need certification. A presentation had been prepared for the KAMs' internal use only. This had been certified. A spreadsheet setting out participants' views had also been circulated to the KAMs. Astellas had not approved circulation of this material to the representatives and it had not been certified. The Panel was very concerned at the nature and level of the detail provided to the KAMs. It did not consider that the provision of such reports to the sales force was consistent with the agreement that transcripts from the advisory board could be used for Astellas' internal business purposes. The presentation and spreadsheet detailed feedback ranking ie from 0, limited use of echinocandins (caspofungin only); ignorant of Mycamine to 10, Mycamine on formulary; use of Mycamine; on message; willing to advocate to others. The data showed that compared to baseline the ranking had improved after the first advisory board and further gains had been made following the second advisory board meeting. The feedback ranking summary slide was headed 'Raise awareness and create motivation to support/prescribe Mycamine' and stated '93% positive shift of opinion towards Mycamine'. The Panel considered that the data produced as an outcome of the advisory board and shared with the sales force reinforced the impression that the purpose of the advisory board was, at least in part, to change the views of participants regarding Mycamine ie to promote the product rather than

just elicit views and advice. The Panel acknowledged that any advisory board on a particular medicine would inevitably have some promotional impact on the participants. In the Panel's view, however, that such impact was evaluated and then communicated to the field force demonstrated an intention to promote Mycamine and positively change participants' views about the product.

The agenda and objectives as described to participants were not necessarily unacceptable. The selection criteria communicated to the KAMs, namely that the company expected advisory board members to *inter alia*, become brand advocates, was not an acceptable outcome for a genuine advisory board. The Panel considered that the provision of detailed information regarding advisory board members' position with regard to their personal use of Mycamine to the MSL managers and the KAMs (who promoted the medicine) was unacceptable as was the failure to certify briefing material for the representatives. The Panel also considered that the roles of the KAMs and MSL staff before and after the meetings were inappropriate and inconsistent with the non-promotional purpose of an advisory board. In the Panel's view the overall arrangements for the advisory boards showed that they had, at least in part been held for a promotional purpose and to develop brand advocates/opinion leaders rather than solely for gathering expert advice and opinion. Thus the Panel ruled that the overall arrangements for the advisory boards were disguised promotion in breach of Clause 12.1. The payment of a fee to attend a promotional event was unacceptable and the fee was in effect an inducement to prescribe, administer or recommend a medicine. A breach of Clause 18.1 was ruled.

The Panel considered that, given the overall arrangements for the advisory boards, Astellas had also failed to comply with the requirements of Clause 20. It was not a genuine consultancy arrangement given the discrepancy between the internal and external documentation and the involvement of the KAMs and MSLs. The Panel was also concerned that the hiring of the health professional might be in effect an inducement to prescribe, administer or recommend Mycamine. A breach of Clause 20 was ruled.

The Panel considered that the overall arrangements had not maintained a high standard and thus a breach of Clause 9.1 was ruled. With regard to Clause 2, the Panel noted that this was reserved for use as a particular sign of censure. The Panel considered that the overall arrangements, particularly the development of brand advocates under the guise of an advisory board, brought discredit upon and reduced confidence in the pharmaceutical industry and in that regard ruled a breach of Clause 2.

Complaint received **21 December 2009**

Case completed **16 March 2010**

CASE AUTH/2291/1/10

HOSPITAL CONSULTANT v FLYNN

Promotion of Actiq

A hospital consultant complained about the use of Davies *et al* (2009) in an advertisement for Actiq (oral transmucosal fentanyl citrate) emailed by Flynn Pharma. Actiq was indicated for the management of breakthrough pain (BTP) in patients already receiving maintenance opioid therapy for chronic cancer pain.

The complainant alleged that the advertisement misrepresented Davies *et al*, which gave a task group's recommendations on the management of cancer related BTP, by focusing on a sub-section of one of the recommendations and ignoring the other eleven. An uninformed reader might believe that the paper recommended Actiq for breakthrough cancer pain, which it did not.

The complainant was also concerned that Christie *et al* (1998), which was the main paper cited in the advertisement, was not an appropriate paper to compare the effects of Actiq vs normal treatment. Actiq was titrated to maximal effect but the data on the normal treatment was derived from the screening phase of the study ie the study did not compare like with like! Indeed, Christie *et al* was much more positive about the effects of Actiq than other published papers.

The detailed response from Flynn is given below.

The Panel noted the headline of the advertisement 'The Task Group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland have called for the management of cancer related breakthrough pain to be individualised'. The advertisement listed factors relevant to the optimal management of cancer related BTP. A statement in an emboldened typeface then read 'Immediate release (IR) oral opioids are not the optimal rescue medication for most episodes of cancer related BTP'. The pharmacokinetic/pharmacodynamic profiles of oral opioids were then discussed followed by two bullet points highlighting when immediate release oral opioids might be useful. The next paragraph in the same colour and size typeface read 'Actiq (oral transmucosal fentanyl citrate) – Established evidence of efficacy'.

A highlighted box at the bottom of the page listed a number of claims for Actiq – including that it had been demonstrated to have pharmacokinetics tailored to the profile of cancer related BTP. An accompanying graph adapted from Christie *et al* compared the pain intensity difference of [Actiq] with patients' usual BTP medication. A banner 'Actiq, Give them a handle on pain' with a link to prescribing information appeared at the end of the advertisement.

The Panel noted that Davies *et al*, on the basis of a literature review, were unable to make recommendations about any individual interventions but did make recommendations about certain generic strategies. Recommendation eight was that opioids were the rescue medication of choice in the management of breakthrough cancer pain. The Panel noted that fentanyl citrate was discussed but no specific recommendations were made, as acknowledged by Flynn.

Overall, the Panel did not consider it unreasonable for the advertisement to focus on one particular area of interest in the management of BTP. In that regard the Panel did not consider that the advertisement was misleading as alleged. No breach of the Code was ruled. However the Panel considered that the design and content of the advertisement implied that Davies *et al* recommended Actiq for use in BTP and that was not so. The claim 'Actiq …. Established evidence of efficacy' was presented immediately after the data from Davies *et al* and appeared to be part of the task group's recommendations. The design of the material was such that there was insufficient differentiation between the recommendations of Davies *et al* and promotional claims for Actiq. The advertisement was misleading and not capable of substantiation in this regard as alleged and breaches of the Code were ruled.

The Panel noted that a graph adapted from Christie *et al* showed a statistically significant difference in pain intensity at 15, 30 and 60 minutes in favour of Actiq vs usual BTP medication. No further details about Christie *et al* were provided. The Panel noted that a secondary objective of Christie *et al* was to compare the efficacy produced by Actiq with that of the patients' usual BTP medication in an open label manner. Assessment of patients' BTP and usual medication occurred during the baseline phase after which the dose-response relationship of Actiq was assessed.

The Panel noted that Christie *et al* was not designed to rigorously compare the usual breakthrough medication and Actiq. The usual breakthrough medication was not titrated as part of the study. The better efficacy of Actiq could thus relate to the suboptimal dose of the usual breakthrough medication. The study authors noted that their results should be considered tentative. Further blinded studies were needed before it could be concluded that Actiq produced better efficacy than patients' usual medication. The Panel thus considered that the graph gave a misleading impression of the comparative efficacy of Actiq which was incapable of substantiation as alleged.

Breaches of the Code were ruled.

Upon appeal by Flynn the Appeal Board noted the highlighted box at the bottom of the advertisement listed a number of claims for Actiq under the heading 'Actiq has been demonstrated:'. The second claim 'To provide rapid analgesia' and the third claim 'To have a short duration of action' were both referenced to Christie *et al,* Portenoy *et al* (1999), Farrar *et al* (1998) and Coluzzi *et al* (2001). The claim 'To provide rapid analgesia' was followed by two sub-claims '0-to 15-minute *Pain Intensity score* was over 2 ½ times larger than the score for usual BTP medication' and '0-to 15-minute *Pain Relief* score was more than *2 times higher* than the score for usual BTP medication' both referenced only to Christie *et al*. Flynn submitted that these sub-claims were quotations from Christie *et al*. They were not presented as such in the advertisement at issue. The graph at issue appeared next to the claims and depicted a statistically significant difference in pain intensity at 15, 30 and 60 minutes in favour of Actiq vs usual BTP medication.

The Appeal Board noted Farrar *et al* which compared Actiq and placebo had, as expected, shown a difference in favour of Actiq. However, both Portenoy *et al* (usual breakthrough medicine vs Actiq) and Coluzzi *et al,* (morphine sulphate immediate release vs Actiq), found a similar pattern of results to Christie *et al* in that Actiq produced a greater and more rapid onset of analgesia in the first hour following administration. Portenoy *et al* and Christie *et al* were both dose titration studies not intended to rigorously compare the analgesic efficacy of Actiq with usual rescue medication. At each time point measured in Christie *et al* and Coluzzi *et al* the pain intensity difference produced by Actiq was reported to be statistically significantly greater than that produced by the active comparator.

The Appeal Board considered that despite caveats in Christie *et al,* the fact that the study was not inconsistent with the available evidence meant that the graph did not mislead as to the comparative efficacy of Actiq vs usual BTP medicine. The graph could be substantiated. The Appeal Board ruled no breaches of the Code.

A hospital consultant complained about the use of Davies *et al* (2009) in an advertisement (ref ACT1809) for Actiq (oral transmucosal fentanyl citrate) emailed by Flynn Pharma Ltd.

Actiq was indicated for the management of breakthrough pain (BTP) in patients already receiving maintenance opioid therapy for chronic cancer pain.

COMPLAINT

The complainant alleged that the advertisement misrepresented Davies *et al* by focusing on a sub-section of one of the recommendations for management and ignoring the other eleven. Indeed, an uninformed reader could be led to believe that the task group recommended Actiq for breakthrough cancer pain, which it did not.

The complainant was also concerned about the use of data from research studies to support the use of Actiq in clinical practice. Christie *et al* (1998), which was the main paper cited in the advertisement, was not an appropriate paper to compare the effects of Actiq vs normal treatment. Actiq was titrated to maximal effect, and the data on the normal treatment was derived from the screening phase of the study ie the study did not compare like with like! Indeed, Christie *et al* was much more positive about the effects of Actiq than other published papers.

When writing to Flynn the Authority asked it to respond in relation to Clauses 1.7, 7.2, 7.4 and 9.1.

RESPONSE

Flynn noted that the advertisement in question (Management of breakthrough pain (BTP)) was supported by nine references, the first of which was Davies *et al*. This was an important publication that made a significant contribution to the knowledge base in the field and Flynn was understandably keen, if not obliged, to make its promotional representations consistent with the teachings of the task group. The advertisement in question was approximately one-page of A4 supported by the addition of prescribing information. A number of points were made about the optimal management of cancer related BTP and the place of immediate release oral opioids in its management which were very clearly referenced to Davies *et al*. There was no attempt to disguise or misrepresent their origin or to imply that any statement referenced had particular or even general applicability to Actiq. The references to and quotes derived from the paper were very limited. Given that Davies *et al* was a set of guideline recommendations, there was a common interest in their widespread recognition, reference and where possible, adoption or integration into practice which Flynn supported. Only very limited use had been made of statements contained within the paper, and that these were accurately reproduced was important. The messages from Davies *et al* were clearly separate from statements relating to Actiq which appeared in separate sections of the advertisement and were separately referenced. No statement linked a reference to the task group findings to any claim about Actiq. Should there be, Flynn would share the complainant's concern as the task group's recommendations stopped short of mentioning any product in particular.

Whilst Flynn believed these arguments addressed the question of misrepresentation in part, the complainant was concerned that the company had focussed on only one recommendation and ignored the others. Flynn noted that the material at issue was an advertisement which set out and supported a few specific claims and points about Actiq; it was

not a review of the management of BTP or indeed a review of the task group's recommendations. It was reasonable, justified and understandable that it focused on a particular issue or aspect of care rather than précis or review the full paper. This did not amount to misrepresentation either by virtue of its selective but accurate use of limited parts of the paper, or possibly in misrepresenting the views of the authors insofar as its use did not reflect the totality of their views.

Flynn noted the complainant's concern about the use of Christie *et al* as 'the main paper cited in the advertisement'. Christie *et al*, however, was one of six references cited in support of the Actiq claims, although it was the only one from which a figure was taken (Pain Intensity Difference (adapted from Christie *et al*)). Four of the cited references, including Christie *et al*, were also cited in Davies *et al* and as such were deemed 'relevant' papers by the task group. Thus, not withstanding that the advertisement was short and few claims were made, all without exception were expressly and clearly referenced and in Flynn's view complied with the requirements of Clause 7.4 that 'any information, claim or comparison must be capable of substantiation'.

The complainant was concerned about Christie *et al* as the pain intensity difference comparisons of Actiq and usual breakthrough medication (reported in the paper and referred to in the advertisement in question) were biased in favour of Actiq. The reasoning given was that the usual breakthrough medication dose data were derived from the baseline phase, but the Actiq doses were determined following a dose titration in the second phase of the study.

However, one of the eligibility criteria for patients entering the study was that they had 'stable pain, defined as persistent pain, no more than moderate on average, tolerable opioid side effects, and the use of four or fewer doses of opioid medication for breakthrough pain daily'. The key take-home message was that patients were 'stable' and pain management was under control. This inferred that whatever their previous or usual BTP medication was, it was sufficient to meet treatment goals and was near optimal.

When they entered the second phase of the study, patients would receive Actiq for the first time for BTP management and the study methodology directed that 'patients were titrated to an effective dose of [Actiq] and the performance of this dose was evaluated'. An 'effective' dose was not synonymous with a dose 'titrated to maximal effect' as the complainant suggested, and there was no evidence in the paper to indicate that study investigations expressly sought to achieve higher levels of control than in the baseline case. Dose titration was to a level that gave appropriate pain control, with acceptable side effects. Flynn noted that most patients were dosed on 200mcg (49%) and out of all patients, 64% were on either 200mcg or 400mcg, the two lowest available doses of Actiq.

Flynn did not therefore consider that Christie *et al* reported an unfair comparison and nor was it the main paper relied upon in support of the claims made.

PANEL RULING

The Panel noted that the prominent blue banner headline of the advertisement read 'The Task Group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland have called for the management of cancer related breakthrough pain (BTP) to be individualised'. The advertisement began by listing factors relevant to the optimal management of cancer related BTP. A statement in an emboldened typeface then read 'Immediate release (IR) oral opioids are not the optimal rescue medication for most episodes of cancer related BTP'. The pharmacokinetic/ pharmacodynamic profiles of oral opioids were then discussed followed by two bullet points highlighting when immediate release oral opioids might be useful. The next paragraph in the same colour and size typeface read 'Actiq (oral transmucosal fentanyl citrate) – Established evidence of efficacy'.

A highlighted box at the bottom of the page listed a number of claims for Actiq – including that it had been demonstrated to have pharmacokinetics tailored to the profile of cancer related BTP. An accompanying graph adapted from Christie *et al* compared the pain intensity difference of transmucosal fentanyl [Actiq] with patients' usual BTP medication. A banner 'Actiq, Give them a handle on pain' with a link to prescribing information appeared at the end of the advertisement.

The Panel noted that Davies *et al*, on the basis of a literature review, were unable to make recommendations about any individual interventions but did make recommendations about certain generic strategies. Recommendation eight was that opioids were the rescue medication of choice in the management of breakthrough cancer pain. The Panel noted that fentanyl citrate was discussed but no specific recommendations were made, as acknowledged by Flynn.

Overall the Panel did not consider it unreasonable for the advertisement to focus on one particular area of interest in the management of BTP. In that regard the Panel did not consider that the advertisement was misleading as alleged. No breach of Clause 7.2 was ruled. However the Panel considered that the design and content of the advertisement implied that Davies *et al* recommended Actiq for use in BTP and that was not so. The claim 'Actiq …. Established evidence of efficacy' was presented immediately after the data from Davies *et al* and appeared to be part of the task group's recommendations. The design of the material was such that there was insufficient

differentiation between the recommendations of Davies *et al* and promotional claims for Actiq. The advertisement was misleading and not capable of substantiation in this regard as alleged and a breach of Clauses 7.2 and 7.4 was ruled. This ruling was not appealed.

The Panel noted that a graph adapted from Christie *et al* showed a statistically significant difference in pain intensity at 15, 30 and 60 minutes in favour of Actiq vs usual BTP medication. No further details about Christie *et al* were provided. The Panel noted that a secondary objective of Christie *et al* was to compare the efficacy produced by Actiq with that of the patients' usual breakthrough pain medication in an open label manner. Assessment of patients' BTP and usual medication occurred during the baseline phase after which the dose-response relationship of Actiq was assessed.

The Panel noted that Christie *et al* stated that the study was not designed to rigorously compare the usual breakthrough medication and Actiq. The usual breakthrough medication was not titrated as part of the study. The better efficacy of Actiq could thus relate to the suboptimal dose of the usual breakthrough medication. The study authors noted that their results should be considered tentative. Further blinded studies were needed before it could be concluded that Actiq produced better efficacy than patients' usual medication. The Panel thus considered that the graph gave a misleading impression of the comparative efficacy of Actiq which was incapable of substantiation as alleged. A breach of Clauses 7.2 and 7.4 was ruled. This ruling was appealed.

APPEAL BY FLYNN

Flynn noted that in reaching its determination the Panel had drawn on and specifically quoted, albeit in the narrowest of terms, only from Christie *et al* notwithstanding that Christie *et al* was one of a number of supporting references. From the discussion section of that paper, the Panel had quoted: 'This study was not designed to compare rigorously the usual breakthrough pain medication and Actiq' and 'The better efficiency of Actiq **could** relate to suboptimal dose selection for the usual breakthrough medicine'(emphasis added) and finally that 'These results should be considered tentative. Further blinded studies will be needed before it can be concluded that Actiq produces better efficacy than patients' usual medication'.

Flynn submitted that the test or case at issue was the extent to which the data and material derived from Christie *et al*, did or did not give a misleading impression (Clause 7.2), and secondly, the extent to which the promotional claims were, or were not capable of substantiation (Clause 7.4).

Flynn noted that in the advertisement, immediately above the boxed data and graph at issue was the claim 'Actiq (oral transmucosal fentanyl citrate) - Established evidence of efficacy'. Within the box itself in the left hand panel, was the bold heading 'Actiq has been demonstrated:' below which four bullet points set out various claims. The graph adapted from Christie *et al* appeared in the right-hand panel of the boxed information and Christie *et al* was referenced to support the first two of the four claims made.

Flynn submitted that the question to consider was what was the established evidence of efficacy relied upon and referenced to demonstrate or support the claims made? Was it unfair, insufficient and overly narrow to only consider Christie *et al* as supporting evidence? Eight references, including six which provided clinical data and/or commentary, were clearly cited, using superscripted annotations against each claim. Flynn did not rely solely or even in large part on just the evidence of Christie *et al* in the substantiation of any claim(s).

Flynn noted that the first of the four claims made was that (Actiq has been demonstrated:) 'To have pharmacokinetics tailored to the profile of cancer related BTP'. The claim was referenced to Portenoy and Hagen (1990) and Streisand *et al* (1991). Portenoy and Hagen stated that an onset of pain within 3 minutes was described in 43% of pains, the median duration of pains was 30 minutes (range 1-240 mins) and further that, 41% of pains were characterised by both rapid onset and brief duration. Streisand *et al* discussed the absorption and bioavailability of oral transmucosal fentanyl citrate and, *inter alia*, reported that peak plasma concentrations of fentanyl were statistically significantly higher and occurred sooner (P=0.003). Thus on balance, Flynn submitted that the references to the claim supported it. Particularly, Portenoy and Hagen and Streisand *et al* highlighted the relevance of events within the first 30 minutes of onset of an episode of BTP. Although the Panel rulings and complaint had not alleged or ruled a breach in regard to the claim, it was pertinent to highlight the point as the claims themselves, to have proper meaning, were related, notwithstanding that they each stood independently. They were grouped together and the design was such that they would be read and considered together, notwithstanding that each was capable of substantiation. It was noted that the first claim did not rely on Christie *et al*.

Flynn noted the second and third claims, which it considered together since both included Christie *et al* as one of a number of supporting references, the advertisement read (Actiq has been demonstrated:) 'To provide rapid analgesia' and 'To have a short duration of action'. Each of these claims was referenced to Christie *et al*, Portenoy *et al* (1999), Farrar *et al* (1998) and Coluzzi *et al* (2001). Collectively, these references constituted the supporting evidence relied upon. Portenoy *et al* and Coluzzi *et al* post-dated Christie *et al* and thus contributed to the knowledge base that Christie *et al* had alluded to in its comment that 'Further blinded studies will be needed before it can be concluded that transmucosal fentanyl produces better efficacy

than patients' usual medication. Flynn stressed that it did not rely on Christie *et al* alone.

Flynn submitted that the claims were supported by all of the cited references and were accurate, balanced, fair and unambiguous and based on an up-to-date evaluation of all the evidence. Christie *et al* did not stand alone or apart in terms of its learning points – indeed the broad findings of Christie *et al* were consistent with, and sat within the range of findings of the four papers as the subsequent arguments would illustrate. Christie *et al*, irrespective of design features and details of the study itself, was representative of the literature evidence. Further, to the extent that its findings were consistent with the later studies, Christie *et al* could be relied upon and regarded as representative of the balanced literature on the subject.

Christie *et al* reported a study of oral transmucosal fentanyl citrate for the treatment of BTP in cancer patients using transdermal fentanyl citrate for persistent pain. Sixty-two patients were randomised and Christie *et al* reported the findings in 47 who completed the study per protocol. The paper reported that eligible patients had stable pain and that they experienced four or fewer episodes of BTP daily. The management of their BTP was evaluated initially over a two day period in the baseline phase of the study, in which the pain was managed with their usual BTP medication. Following the baseline phase, patients were introduced to and titrated to an appropriate dose of Actiq in the Actiq phase of the study, and the management of BTP was further assessed over a second two day period. Two widely used measures of analgesia, Pain Intensity Difference (PID) and Pain Relief (PR), were evaluated at time points of 15, 30, 45 and 60 minutes. The graph of PID data derived from Christie *et al* formed the right-hand part of the boxed information and accurately reflected that data as reported by Christie *et al*. Flynn noted that a footnote made it clear the graph was adapted from Christie *et al*.

Flynn submitted that the complaint, and presumably an influencing factor on the Panel in reaching its conclusions, was that it was unreasonable to compare the pain measures from the baseline phase (on usual background medication) to those in the Actiq phase, where patients were titrated to an effective dose. The complainant was concerned that the usual baseline medication dose might be suboptimal and/or that the data were flattered by the titration of Actiq to an optimal dose, such that the product benefits (in terms of PID and PR measures) were misleadingly and unduly exaggerated. On the evidence of Christie *et al* and the other three supporting references Flynn rejected these concerns.

Flynn submitted that in Christie *et al* 19/47 (40%) patients completing the study used only the lowest dose of Actiq (200mcg) and 30/47 (64%) used either 200mcg or 400mcg (the next highest strength available from a range of six product strengths in the dose range 200mcg – 1600mcg). Further, patients entering the study had stable pain and could thus be regarded as relatively well-managed and by interference then, receiving BTP medication that was generally appropriate and effective. In other words, their dose of usual breakthrough medication was generally considered adequate.

Flynn submitted that it was important to consider whether the design of Christie *et al* was biased in favour of Actiq, to the extent that it presented an unduly or misleading favourable effect of Actiq. Portenoy *et al* (n = 48 vs n = 47 in Christie *et al*) reported a controlled dose titration study of Actiq in breakthrough pain in cancer patients. Key observations pertinent to the product claims at issue, reported in that study were:

- Pain intensity scores of approximately 6 (0-10 scale) were recorded before Actiq dose
- 60 minutes post-dose, average pain intensity scores were 1.5
- The pain intensity reduction with Actiq in 15 minutes was 56% of the total pain intensity decline
- The pain intensity reduction with usual medication (rescue) in 15 minutes was 32% of the total.

Flynn submitted that in other words, nearly half of the total reduction in pain intensity following dosing with Actiq, was realised in the first 15 minutes. Secondly, the reduction in pain intensity in 15 minutes following Actiq was 1.75 times that of the usual rescue medication (56/32). This compared favourably with the observation reported by Christie *et al* although one must caution against making direct comparison of efficacy endpoints from studies conducted by different investigators, at different times in different patient populations. The take-home message of both studies was simply that significant advantages in terms of pain intensity were realised in the 0-15 minute period with Actiq.

Flynn noted that Farrar *et al* concluded that '[Actiq] produced significantly larger changes in pain intensity and better pain relief than placebo at all time points'. Farrar *et al* studied PID at 15, 30, 45 and 60 minutes in a per protocol population of 86 patients. PID15 and PID30 scores for Actiq were both 159% greater than placebo at the same time points.

Coluzzi *et al* reported a randomised trial comparing Actiq and morphine sulphate immediate release (MSIR) and obtained data in 75 evaluable patients. The PID15 score was the primary efficacy variable. The authors concluded that '[Actiq] yielded outcomes (PI, PID and PR) at all time points that were significantly better then MSIR.' and that '[Actiq] was more effective that MSIR in treating breakthrough cancer pain'.

Finally Flynn noted that Davies *et al* identified Christie *et al*, Portenoy *et al*, Portenoy and Hagen and Coluzzi *et al* but not Farrar *et al* as 'relevant' papers. That was, three of the four references cited

by Flynn to substantiate claims were identified by Davies *et al* and used in some part to inform and shape its findings. Indeed the same three references were specifically referred to collectively in Section 3.8 of Davies *et al* as 'controlled trials'. There was no comment as to methodological weaknesses or differences in these studies.

In conclusion, Flynn submitted that breaches of Clause 7.2 and 7.4 should be overruled. The arguments above made it clear that the findings of Christie *et al* were consistent with the broader literature on which Flynn also relied and referenced in supporting the claim that Actiq provided rapid analgesia in the 0-15 minute period. Christie *et al* was only one of a number of studies that was recognised and widely cited and Flynn was justified in using it.

COMMENTS FROM THE COMPLAINANT

There were no further comments from the complainant.

APPEAL BOARD RULING

The Appeal Board noted that the advertisement at issue was emailed to pain specialists that had previously consented to being sent promotional material by email.

The Appeal Board noted the highlighted box at the bottom of the advertisement listed a number of claims for Actiq under the heading 'Actiq has been demonstrated:'. The second claim 'To provide rapid analgesia' and the third claim 'To have a short duration of action' were both referenced to Christie *et al*, Portenoy *et al*, Farrar *et al* and Coluzzi *et al*. The claim 'To provide rapid analgesia' was followed by two sub-claims '0-to 15-minute **Pain Intensity score** was over **2 ½ times larger** than the score for usual BTP medication' and '0-to 15-minute **Pain Relief score** was more than **2 times higher** than the score for usual BTP medication' both referenced only to Christie *et al*. Flynn submitted that these sub-claims were quotations from Christie *et al*. They were not presented as direct quotations in the advertisement at issue. The graph at issue appeared next to the claims and depicted a statistically significant difference in pain intensity at 15, 30 and 60 minutes in favour of Actiq vs usual breakthrough pain medication. The graph was referenced as being adapted from Christie *et al*.

The Appeal Board noted Farrar *et al* which compared Actiq and placebo had, as expected, shown a difference in favour of Actiq. However, both Portenoy *et al*, that compared usual breakthrough medicine against Actiq, and Coluzzi *et al*, that compared morphine sulphate immediate release with Actiq, found a similar pattern of results to Christie *et al* in that Actiq produced a greater and more rapid onset of analgesia in the first hour following administration. Portenoy *et al* and Christie *et al* were both dose titration studies not intended to rigorously compare the analgesic efficacy of Actiq with usual rescue medication. At each time point measured in Christie *et al* and Coluzzi *et al* the pain intensity difference produced by Actiq was reported to be statistically significantly greater than that produced by the active comparator.

The Appeal Board considered that despite the authors' concerns with regard to Christie *et al*, the fact that the study was not inconsistent with the available evidence meant that the graph did not mislead as to the comparative efficacy of Actiq vs usual breakthrough pain medicine. The graph could be substantiated. The Appeal Board ruled no breach of Clauses 7.2 and 7.4 of the Code. The appeal on this point was successful.

Complaint received	**4 January 2010**
Case completed	**21 April 2010**

CASE AUTH/2293/1/10

VOLUNTARY ADMISSION BY FERRING

Pentasa abbreviated advertisement

Ferring voluntarily admitted that a Pentasa (mesalazine) abbreviated advertisement published in the programme for Gastro 2009 breached the Code. The advertisement had been placed by colleagues in global marketing Switzerland, who failed to put it through the UK approval procedure. This omission was regretted and steps were being undertaken to emphasise the need for UK approvals.

Ferring acknowledged that the claim, 'the power of five in ulcerative colitis', did not adequately describe the approved UK indications for Pentasa. The UK licensed indication was restricted to mild to moderate ulcerative colitis and the advertisement should have stated this to avoid possible breaches of the Code.

Ferring acknowledged that the adverse event statement was not in line with the Code.

Ferring submitted that 'excellent' in the claim 'Celebrate PODIUM – a study demonstrating excellent clinical efficacy' was in breach because it was ambiguous and gave an exaggerated impression of Pentasa's properties which could not be substantiated.

The action to be taken by the Authority in relation to a voluntary admission was set out in its Constitution and Procedure which stated, *inter alia*, that the Director should treat an admission as a complaint if it related to a serious breach. As failure to certify promotional material and promotion inconsistent with the summary of product characteristics (SPC) were involved, which were serious matters, the Director decided that the admission must be treated as a complaint.

The detailed response from Ferring is given below.

The Panel noted that it was an established principle under the Code that UK companies were responsible for the acts and omissions of their overseas affiliates that came within the scope of the Code. The Panel noted that the UK company had made it clear to global marketing in Switzerland that the advertisement needed to comply with the UK Code including the requirement for certification. Unfortunately this had not happened.

The Panel noted that the advertisement was about the Pentasa range of products. Pentasa enema could be used to treat ulcerative colitis in the distal colon and rectum, and Pentasa tablets could be used to maintain remission in ulcerative colitis otherwise the Pentasa range was indicated for the treatment of mild to moderate ulcerative colitis. The unqualified reference to 'ulcerative colitis' in the advertisement was thus inconsistent with the Pentasa SPCs and misleading in that regard. The Panel ruled breaches of the Code as acknowledged by Ferring.

The Panel ruled that the statement regarding adverse event reporting did not use the obligatory text and was in breach of the Code as acknowledged by Ferring.

The Panel considered that the unqualified claim 'excellent clinical efficacy' was ambiguous and gave an exaggerated impression of Pentasa which could not be substantiated. Breaches of the Code were ruled as acknowledged by Ferring.

The Panel noted that material that had not been certified had been used in the UK. The Panel noted its rulings above of breaches of the Code. The Panel considered that high standards had not been maintained and a breach of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

VOLUNTARY ADMISSION

Ferring Pharmaceuticals Ltd voluntarily admitted that a Pentasa (mesalazine) abbreviated advertisement (ref H53261 UEGW A5 Pentasa v4. indd 1) was in breach of several clauses of the Code. The advertisement had appeared in the programme for Gastro 2009, an independent gastroenterology conference held in London, 21-25 November 2009. The programme was intended for health professionals. Ferring UK became aware of the advertisement in December.

Ferring explained that the advertisement had been placed by colleagues from global marketing in Ferring's Swiss headquarters, who failed to put it through the UK approval procedure. This omission was regretted and steps were being undertaken to emphasise the need for UK approvals of all items where required.

Ferring submitted that the heading, 'the power of five in ulcerative colitis', was an international strapline used in a number of markets outside the UK. Ferring acknowledged that 'ulcerative colitis' did not adequately describe the approved UK indications for Pentasa. In the UK, the licensed indication was restricted to mild to moderate ulcerative colitis and had the advertisement been subject to UK approval, the heading would have

been modified to include the term 'mild to moderate' to avoid possible breaches of Clauses 3.2 and 7.2.

With regard to the adverse event statement Ferring acknowledged that the final sentence, 'Adverse events should also be reported to Ferring Pharmaceuticals Ltd' was omitted in breach of Clause 5.6.

Ferring submitted that the 'excellent' in the claim 'Celebrate PODIUM – a study demonstrating excellent clinical efficacy', which appeared beneath the product logo, was in breach of Clauses 7.2, 7.4 and 7.10 because it was ambiguous and gave an exaggerated impression of Pentasa's properties which could not be substantiated.

* * * * *

The action to be taken by the Authority in relation to a voluntary admission was set out in Paragraph 5.4 of the Constitution and Procedure which stated, *inter alia*, that the Director should treat an admission as a complaint if it related to a serious breach. As failure to certify promotional material and promotion inconsistent with the summary of product characteristics (SPC) were involved, which were serious matters, the Director decided that the admission must be treated as a complaint. When writing to Ferring, the Authority asked it to respond in relation to Clauses 2, 3.2, 5.6, 7.2, 7.4, 7.10 and 9.1 of the Code.

RESPONSE

Ferring submitted that in July 2009, Ferring global marketing asked for its advice on an early draft of the advertisement which Ferring global had prepared in collaboration with a UK advertising agency. Ferring UK advised that the draft required modification to comply with UK requirements and that the updated advertisement would be subject to UK sign-off. The draft version of the advertisement was sent to the Gastro 2009 committee as a 'place holder' by the advertising agency. A change in personnel at the agency and a lapse in handover procedures meant that this particular item was not tracked appropriately. As a result, the original, draft version of the advertisement was printed in the Gastro 2009 programme. No final certification or go-ahead for this item was given by Ferring UK.

Ferring did not believe that there had been a breach of Clause 2, which related to promotional activities or materials that brought discredit upon, or reduced confidence in, the pharmaceutical industry, either by positive action or inadequate action. Ferring noted that a breach of Clause 2 denoted particular censure and did not believe that the circumstances surrounding this event related in type or scale to the examples of activities which could lead to a breach of this clause.

Ferring believed that the advertisement might be in breach of Clause 3.2 since 'ulcerative colitis', in the international strapline 'the power of five in ulcerative colitis', might not adequately describe the approved UK indications for Pentasa. In the UK, Pentasa tablets were indicated for the treatment of mild to moderate exacerbations of ulcerative colitis and for the maintenance of remission of ulcerative colitis. Pentasa sachets were indicated for mild to moderate ulcerative colitis. In addition the Pentasa enema was indicated for the treatment of ulcerative colitis affecting the distal colon and rectum.

In 2008, during inter-company communication with Shire Pharmaceuticals Ltd about an item promoting Pentasa sachets, Ferring UK agreed not to use 'ulcerative colitis' without the clarification of 'mild to moderate'. In the UK, Ferring had taken a conservative approach to the interpretation of these indications and promoted Pentasa for use in mild to moderate ulcerative colitis. If the advertisement now at issue had been subject to UK approval the heading would have been modified to include the term 'mild to moderate' to avoid a possible breach of Clause 3.2. 'The power of five in ulcerative colitis' was used outside the UK and was intended to refer to the Pentasa range of products and not solely to the sachets. Ferring acknowledged that 'ulcerative colitis' might not be considered to appropriately describe the approved indications in the UK for Pentasa. However, the Pentasa range was not restricted to use in only mild to moderate ulcerative colitis. Pentasa tablets were additionally indicated '… for the maintenance of remission of ulcerative colitis', and Pentasa enema was indicated for the treatment of ulcerative colitis affecting the distal colon and rectum.

Ferring acknowledged that the advertisement was in breach of Clause 5.6 as the statement regarding adverse event reporting omitted the final sentence, 'Adverse events should also be reported to Ferring Pharmaceuticals Ltd'.

Ferring believed that the advertisement might be in breach of Clauses 7.2, 7.4 and 7.10 because the claim 'Celebrate PODIUM – a study demonstrating excellent clinical efficacy' was ambiguous and might give an exaggerated impression of the properties of Pentasa. 'Excellent' might be considered to imply a special benefit for Pentasa over other forms of mesalazine, which could not be substantiated.

Ferring believed that this matter was in breach of Clause 9.1; a failure in the system that resulted in the publication of an advertisement that had not been appropriately approved meant that high standards were not maintained. Ferring endeavoured to consistently maintain high standards and regretted this failing.

Ferring stated that it currently used a hard copy sign-off system in the UK. A number of recent product launches had put increased pressure on that system and towards the end of 2009 Ferring decided to introduce an electronic sign-off system in the first quarter of 2010 to further enhance its

sign-off process. Ferring believed that the introduction of this new system would help to reduce the chance of a recurrence of a similar incident.

In addition, Ferring UK had agreed the following actions with its Swiss colleagues:

- The global product manager responsible for the advertisement had been reminded of the importance of following the relevant standard operating procedure (SOP), which was, regrettably, not implemented correctly on this particular occasion.
- Ferring global would review the SOP to see if it needed to be updated.
- All relevant staff in global marketing had been made aware and briefed in detail of the importance of following the SOP.
- There was a plan to ensure all relevant employees had documented evidence of training with regards to this SOP.

PANEL RULING

The Panel noted that it was an established principle under the Code that UK companies were responsible for the acts and omissions of their overseas affiliates that came within the scope of the Code. The Panel noted that the UK company had made it clear to global marketing in Switzerland that the advertisement needed to comply with the UK Code including the requirement for certification. Unfortunately this had not happened.

The Panel noted that the advertisement was about the Pentasa range of products. Pentasa enema could be used to treat ulcerative colitis in the distal colon and rectum, and Pentasa tablets could be used to maintain remission in ulcerative colitis otherwise the Pentasa range was indicated for the treatment of mild to moderate ulcerative colitis. The unqualified reference to 'ulcerative colitis' in the advertisement was thus inconsistent with the indication in the Pentasa SPCs and misleading in that regard. The Panel ruled breaches of Clauses 3.2 and 7.2 as acknowledged by Ferring.

The Panel noted that the statement regarding adverse event reporting read 'Adverse events should be reported. Information about adverse event reporting can be found at www.yellowcard.gov.uk'. The obligatory text as stated in Clause 5.6 was 'Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to [relevant pharmaceutical company]'. The Panel considered that the failure to use the obligatory text was in breach of Clause 5.6 as acknowledged by Ferring. A breach of Clause 5.6 was thus ruled.

The Panel considered that the unqualified claim 'excellent clinical efficacy' was ambiguous and gave an exaggerated impression of Pentasa which could not be substantiated. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled as acknowledged by Ferring.

The Panel noted that material that had not been certified had been used in the UK. The Panel noted its rulings above of breaches of the Code. The Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

Proceedings commenced	**11 January 2010**
Case completed	**24 February 2010**

CASE AUTH/2300/2/10

EX-EMPLOYEE v ASTRAZENECA

Legibility of prescribing information

An ex-employee of AstraZeneca queried whether the prescribing information in advertisements for Seroquel XL (quetiapine), Zoladex (goserelin) and Crestor (rosuvastatin), all placed by AstraZeneca in the BMJ, 20 February, was clear and legible as defined in the Code.

The detailed response from AstraZeneca is given below.

The Panel noted that in the Seroquel advertisement the headings of the various sections did not start on a new line and nor were they emboldened. The only way in which the headings had been distinguished from other text was by underlining but this was so faint as to be almost non-existent. The Panel considered that the line length and spacing between the lines meant that, although on the limits of acceptability, overall the prescribing information was legible even if a lower case 'x' was only approximately 1mm in height. However given the difficulty in identifying the various sections of the prescribing information the Panel considered that the prescribing information was not clear and a breach of the Code was ruled.

The Panel noted that in the advertisements for Zoladex and Crestor the section headings were emboldened and underlined and thus readily distinguished from the rest of the text. The Panel considered that in both advertisements the line length and spacing between the lines meant that, although on the limits of acceptability, overall the prescribing information was clear and legible even if a lower case 'x' was only approximately 1mm in height. No breaches of the Code were ruled.

COMPLAINT

An ex-employee of AstraZeneca UK Ltd queried whether the prescribing information in three advertisements placed by AstraZeneca in the BMJ, 20 February, was clear and legible as defined in the Code.

At issue were a double-page Seroquel XL (quetiapine) advertisement (CZ001847f-SERO), a one-page Zoladex (goserelin) advertisement (CZ001970m-ZOLA) and a one-page Crestor (rosuvastatin) advertisement (CZ002029-CRES).

When writing to AstraZeneca, the Authority asked it to respond in relation to Clause 4.1 of the Code.

RESPONSE

AstraZeneca submitted that it recognized that the prescribing information was essential information and therefore this had been provided in a clear and legible manner for all three advertisements. AstraZeneca did not understand how the prescribing information for these advertisements was not clear and legible.

Seroquel XL advertisement

AstraZeneca stated that the prescribing information was an integral part of the advertisement and was positioned across the bottom of both pages for ease of reference. It was clear, legible and readable. Legibility had been achieved with a lower case 'x' approximately 1 mm in height, a line size of 80 characters including spaces, and an appropriate choice of font style (Helvetica Roman). Readability was enhanced by the choice of colour contrast with white type on a black background for maximum contrast, clear spacing of columns and clear spacing between lines. Therefore, AstraZeneca did not agree that the prescribing information in this advertisement was not clear and legible as alleged and therefore was not in breach of Clause 4.1.

Zoladex advertisement

Similarly, the prescribing information was an integral part of this advertisement and was positioned at the bottom of the page for ease of reference. It was clear, legible and readable. Legibility had been achieved with a lower case 'x' approximately 1 mm in height, a line size of 92 characters including spaces, and an appropriate choice of font style (Avant Garde Gothic). Readability was enhanced by the choice of colour contrast with black type on a yellow background, clear spacing of columns, clear spacing between lines and by use of emboldened headings. Therefore, AstraZeneca did not agree that the prescribing information in this advertisement was not clear and legible.

Crestor advertisement

Similarly, the prescribing information was an integral part of this advertisement and this time was positioned at the top of the page for ease of reference. It was clear, legible and readable. Legibility had been achieved with a lower case 'x' approximately 1 mm in height, a line size of 87 characters including spaces, and an appropriate choice of font style (Arial). Readability was enhanced by the choice of colour contrast with dark green type on a pale background, clear spacing of columns, clear spacing between lines and by use of emboldened headings. Therefore, AstraZeneca did not agree that the prescribing information in this

advertisement was not clear and legible as implied by the complainant.

PANEL RULING

The Panel noted that Clause 4.1 required the prescribing information to be clear and legible. The supplementary information to Clause 4.1 gave recommendations to help achieve clarity stating that legibility was not simply a question of type size; it recommended that type size should be such that a lower case letter 'x' was not less than 1mm in height and lines should be no more than 100 characters in length. Other factors mentioned were spacing, type style, contrast and emboldening headings and starting each section on a new line.

The Panel considered each advertisement separately.

The Panel noted that in the Seroquel advertisement the headings of the various sections did not start on a new line and nor were they emboldened. The only way in which the headings had been distinguished from other text was by underlining but this was so faint as to be almost non-existent and so it was extremely difficult to find the start of any of the sections. The Panel considered that the line length and spacing between the lines meant that, although on the limits of acceptability, overall the prescribing information was legible even if a lower case 'x' was only approximately 1mm in height. However given the difficulty in identifying the various sections of the prescribing information the Panel considered that the prescribing information was not clear and a breach of Clause 4.1 was ruled.

The Panel noted that in the Zoladex advertisement the section headings were emboldened and underlined and thus readily distinguished from the rest of the text such that it was easy to find the start of any of the sections. The Panel considered that the line length and spacing between the lines meant that, although on the limits of acceptability, overall the prescribing information was clear and legible even if a lower case 'x' was only approximately 1mm in height. No breach of Clause 4.1 was ruled.

The Panel noted that in the Crestor advertisement the section headings were emboldened and thus readily distinguished from the rest of the text such that it was easy to find the start of any of the sections. The Panel considered that the line length and spacing between the lines meant that, although on the limits of acceptability, overall the prescribing information was clear and legible even if a lower case 'x' was only approximately 1mm in height. No breach of Clause 4.1 was ruled.

Complaint received **24 February 2010**

Case completed **26 March 2010**

ANONYMOUS GENERAL PRACTITIONER v LILLY

Alleged promotion of once-weekly Byetta

An anonymous and uncontactable general practitioner alleged that two different representatives from Eli Lilly had told him that a long-acting version of exenatide (Byetta) would be launched in the UK 'within the next couple of months'. From his own research the complainant found that there had been no such application for a product licence in Europe. The complainant felt that was deliberately misleading and disappointing and that Lilly should advise its representatives not to mislead clinicians in this way.

The detailed response from Lilly is given below.

The Panel noted that no information had been provided about the Lilly personnel; there was no way of knowing if they were sales representatives or health development managers. Two local sales representatives from central London had, for the purposes of the Diabetes UK Conference, been briefed on exenatide once-weekly for the first and only time on 2 March 2010, the date that the complaint was received by the Authority. Health development managers had been trained on the product in mid February.

The Panel noted that the Code prohibited the promotion of a medicine prior to the grant of its marketing authorization.

Lilly submitted that its health development managers provided advance notification of the introduction of Byetta once-weekly given that it might significantly affect the budgets of the NHS. The Panel noted that the supplementary information to Clause 3.1 of the Code set out detailed requirements in this regard including that information should be directed to those responsible for making policy decisions on budgets rather than those expected to prescribe. The Panel had no way of knowing the complainant's status in this regard although as a GP it was unlikely that he would direct budgets.

Bearing in mind the lack of evidence from the complainant the Panel decided that the complainant had not proved his complaint on the balance of probabilities. No breach was ruled.

An anonymous and uncontactable general practitioner, complained about comments made by representatives of Eli Lilly and Company Limited about a long acting formulation of Byetta (exenatide).

COMPLAINT

The complainant stated that on a couple of occasions recently two different Lilly representatives had told him that a long-acting version of exenatide would be launched in the UK 'within the next couple of months'. Being active in the treatment of diabetes, the complainant carried out his own internet research to find that there had been no such application for a product licence in Europe. The complainant felt that was deliberately misleading and disappointing.

The complainant did not want to get the representatives concerned into trouble but felt that Lilly should advise its representatives not to mislead clinicians in this way.

When writing to Lilly, the Authority asked it to comment in relation to Clauses 3.1 and 7.2 of the Code.

RESPONSE

Lilly explained that Byetta was available as either a 5mcg or a 10mcg exenatide per dose pre-filled pen and was indicated for treatment of type 2 diabetes in combination with metformin and/or sulphonylureas in patients who had not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. Byetta should be initiated at 5mcg twice daily, for a least one month in order to improve tolerability; the dose could then be increased to 10mcg twice daily to further improve glycaemic control.

Exenatide once-weekly was an extended-release medication for type 2 diabetes designed to deliver continuous therapeutic levels of exenatide in a single weekly dose. Both Byetta and exenatide once-weekly were glucagon-like peptide-1 (GLP-1) receptor agonists.

Exenatide once-weekly was not currently licensed for use. The NDA (New Drug Application) was submitted to the FDA in the US in May 2009 and accepted in July 2009. It was based on data from the DURATION (**D**iabetes therapy **U**tilisation: **R**esearching changes in **A**1C, weight, and other factors **T**hrough **I**ntervention with exenatide **On**ce weekly) clinical trial program. A licence application was submitted to the European Medicines Evaluation Agency (EMEA) in March 2010 and it was anticipated that a European licence would be obtained in 2011.

Lilly submitted that its diabetes sales force was required and instructed to promote only licensed products which included Byetta. To this end, no material had been given to sales representatives which referred to exenatide once-weekly and no

general guidance had been issued about responding to requests from health professionals about any aspect of exenatide once-weekly. The latter, Lilly believed was consistent with its objective of ensuring that all promotion of the GLP-1 receptor agonists was focussed upon and restricted to Byetta. This was evidenced by emails between the Byetta brand manager and the ethics and compliance director.

A specific exception to the above occurred in relation to the Diabetes UK Conference in Liverpool (3 to 5 March 2010). In preparation for this, all Lilly staff attending the conference, including Lilly diabetes representatives, were briefed on 2 March 2010 and provided with strict and explicit guidance about responding to any questions or requests from health professionals about exenatide once-weekly. In particular slides 43 and 44 of the briefing presentation clearly addressed the latter and instructed all staff to inform interested delegates, reactively, that exenatide once-weekly was not a licensed product and then to refer any enquiry about exenatide once-weekly to the Lilly clinical research physicians attending the conference or to the Lilly medical information department. Indeed, all other Lilly staff were also instructed not to engage in any conversation about exenatide once-weekly. This briefing was deemed appropriate and necessary given that diabetologists attending this major specialist/academic meeting would have a legitimate interest in medical and scientific information about products such as exenatide once-weekly or other products in development.

Lilly submitted that given the likelihood that exenatide once-weekly might significantly affect the budgets of NHS organisations, Lilly started, in mid February, to train its health development managers (HDMs) to facilitate the advance notification of the introduction of this new medicine. Importantly, the latter did not involve any member of the Lilly diabetes sales force and only involved named HDMs who were briefed, trained and provided with specific information about exenatide once-weekly, in keeping with the requirements of Clause 3.1 and its supplementary information.

Lilly noted that its sales representatives were fully aware of the Code and were required to abide by it as well as Lilly's own internal standard operating procedures which were based on the Code.

In the absence of any specific details about the complainant, such as their name or location of their surgery, and the specific dates and venues when the alleged discussions took place, Lilly had tried to conduct as full an investigation as possible. Lilly had identified all the relevant members of its sales force who promoted Byetta in the complainant's area. It had discussed the allegations with the national sales manager who had confirmed that there had been no sales force briefing about exenatide once-weekly. Lilly therefore did not expect any of its sales representatives to have discussed exenatide once-weekly as alleged. On this basis Lilly did not accept the complainant's allegations. Lilly categorically refuted the complainant's suggestion that Lilly had intentionally misled him.

Two members of the Lilly diabetes sales force who promoted Byetta in the complainant's area supported Lilly's promotional activity at the Diabetes UK Conference in Liverpool. As discussed previously, they, along with all other Lilly staff attending the conference, were specifically briefed on 2 March 2010 and given strict and clear guidance about responding to any requests from health professionals about exenatide once-weekly. This being the first and only such briefing to involve Lilly sales representatives covering the complainant's area, Lilly noted that the date of the briefing coincided with that of the complaint which referred to two, presumably prior, occasions when Clauses 3.1 and 7.2 were allegedly breached by Lilly sales representatives working in the complainant's area.

Lilly therefore refuted the allegation that its sales representatives had promoted exenatide once-weekly prior to the grant of a marketing authorization and deliberately misled the anonymous complainant. Lilly remained confident of the high standard and quality of all Lilly training and briefing materials and rejected the alleged breach of Clauses 3.1 and 7.2.

If the Authority could provide any further specific details regarding these allegations, Lilly would investigate the matter further.

In conclusion, Lilly was cognisant of its responsibilities with respect to the Code and had ensured that the promotional activities of its sales representatives were consistent with this (including, without limitation, Clauses 3.1 and 7.2) and of the highest standard and quality.

PANEL RULING

The Panel noted that the complainant was anonymous and non contactable. No information had been provided about the Lilly personnel alleged to have promoted exenatide once-weekly. There was no way of knowing if they were sales representatives or health development managers. Two sales representatives from the complainant's area had, for the purposes of the Diabetes UK Conference, been briefed on exenatide once-weekly for the first and only time on 2 March 2010, the date that the complaint was received by the Authority. Health development managers had been trained on the product in mid February.

The Panel noted that the Clause 3.1 prohibited the promotion of a medicine prior to the grant of its marketing authorization.

Lilly submitted that its health development managers provided advance notification of the introduction of Byetta once-weekly given that it might significantly affect the budgets of the NHS.

The Panel noted that the supplementary information to Clause 3.1 of the Code set out detailed requirements in this regard including that information should be directed to those responsible for making policy decisions on budgets rather than those expected to prescribe. The Panel had no way of knowing the complainant's status in this regard although as a GP it was unlikely that he/she would direct budgets.

Bearing in mind the lack of evidence from the complainant the Panel decided that the complainant had not proved his/her complaint on the balance of probabilities. No breach of Clauses 3.1 and 7.2 was ruled.

During its consideration of this case and on the basis of the documents provided, the Panel queried whether the activities of the health development managers met the supplementary information to Clause 3.1, Advance notification of new products or product changes, particularly that in order to provide information to those responsible for policy decisions on budgets, the likely cost and budgetary implications must be indicated and must be such that they will make significant differences to the likely expenditure of health authorities and trust hospitals and the like. Lilly's statement about the cost of the product was equivocal in that there was a **likelihood** that exenatide once-weekly **might** significantly affect NHS budges (emphasis added) and there was no further details in the materials provided to the Panel. The Panel requested that Lilly be advised of its concerns in this regard.

Complaint received	**2 March 2010**
Case completed	**25 March 2010**

CASE AUTH/2302/3/10

SENIOR HOSPITAL PHARMACIST v FERRING

Letter about Glypressin

A senior hospital pharmacist alleged that in a letter about Glypressin Solution for Injection (terlipressin acetate) Ferring was scaremongering and misquoting from a safety alert issued by the National Patient Safety Agency (NPSA) to get extra NHS sales.

The letter stated that the new Glypressin Solution had, *inter alia*, the following advantage: 'Ready to use for injection (The National Patient Safety Agency recommends that only licensed ready-to-administer or ready-to-use injectable medicines are supplied)'. The complainant stated that 'only' misrepresented the NPSA which stated it was 'preferable'. The word 'only' was used by the NPSA but that was not how it was meant.

The complainant provided part of the relevant NPSA patient safety alert 'Promoting safer use of injectable medicines'. A section headed 'Implement a "purchasing for safety" policy to promote procurement of injectable medicines with inherent safety features' stated, *inter alia*, 'It is preferable that only licensed ready-to-administer or ready-to-use injectable medicines are procured and supplied'.

The complainant had asked Ferring to confirm where the NPSA 'recommends that only licensed ready-to-administer …'. In response, Ferring medical information had referred the complainant to the statement in the safety alert that 'It is preferable that only licensed ready-to-administer or ready-to-use injectable medicines are procured and supplied. The NPSA suggests that NHS organisations should work with the pharmaceutical industry to identify new products and formulations that could make practice safer.'

The detailed response from Ferring is given below.

The Panel noted that the NPSA in its patient safety alert, 20 (2007), set out six action points to promote safer use of injectable medicines including 'Implement a "purchase for safety" policy to promote procurement of injectable medicines with inherent safety features'. The further information on that action point recommended firstly that policies should advocate the purchase of injectable medicines that included technical information about their preparation and administration and were designed in such a way as to promote safer practice. This was followed by the advice used as a reference for the material at issue that 'It is preferable that only licensed ready-to-administer or ready-to-use injectable medicines are procured and supplied'. The section then referred to the frequent preparation of an unlicensed injectable medicine from a licensed product and that ready-to-use and ready-to-administer products that could not be prepared in the hospital pharmacy department should be sourced from NHS manufacturing units or commercial 'specials' manufacturers. It was essential that the quality of these medicines was assessed and approved before purchase. The NPSA patient safety alert included guidance on risk assessment and action plans as well as protocols and procedures for preparing and administering injectable medicines.

The Panel considered that it was clear from the patient safety alert that the NPSA's preference was that only licensed ready-to-administer or ready-to-use injectables were procured and supplied. However, the NPSA accepted that sometimes unlicensed medicines needed to be used or those from NHS manufacturing units or commercial 'specials' manufacturers.

The Panel considered that the letter at issue was not sufficiently clear regarding the NPSA advice. The claim in full read 'Ready to use for injection (The National Patient Safety Agency recommends that only licensed ready-to-administer or ready-to-use injectable medicines are supplied)'. In the Panel's view there was a difference between a preference and a recommendation. Further the claim at issue had been derived from one sentence in four paragraphs of text which referred to 'purchasing for safety' policies. The context of the NPSA statement had not been fully reflected. The letter was misleading and not capable of substantiation. Breaches of the Code were ruled.

A senior hospital pharmacist complained about a letter (ref GL/317/02/10) which he had received from Ferring Pharmaceuticals Ltd about Glypressin Solution for Injection (terlipressin acetate). The letter was mailed to NHS hospital pharmacists in February 2010 and concerned the award of a national tender in England via the NHS Purchasing and Supply Agency (PASA) for the supply of Glypressin Solution.

COMPLAINT

The complainant alleged that Ferring was scaremongering and misquoting from a safety alert issued by the National Patient Safety Agency (NPSA) to get extra sales at the expense of the NHS.

The letter stated that the new Glypressin Solution had, *inter alia*, the following advantage: 'Ready to use for injection (The National Patient Safety Agency recommends that only licensed ready-to-administer or ready-to-use injectable

medicines are supplied)'.

The complainant stated that the word 'only' misrepresented the NPSA which stated it was 'preferable'. The word 'only' was used by the NPSA but that was not how it was meant.

The complainant provided part of the relevant NPSA patient safety alert 'Promoting safer use of injectable medicines'. A section headed 'Implement a "purchasing for safety" policy to promote procurement of injectable medicines with inherent safety features' stated, *inter alia*, 'It is preferable that only licensed ready-to-administer or ready-to-use injectable medicines are procured and supplied'.

The complainant had asked Ferring to confirm where the NPSA 'recommends that only licensed ready-to-administer …'. In response, Ferring medical information had referred the complainant to page 4, point 4, paragraph 2 which stated:

> 'It is preferable that only licensed ready-to-administer or ready-to-use injectable medicines are procured and supplied. The NPSA suggests that NHS organisations should work with the pharmaceutical industry to identify new products and formulations that could make practice safer.'

When writing to Ferring, the Authority asked it to comment in relation to Clauses 7.2 and 7.4 of the Code.

RESPONSE

Ferring noted that the letter included three bullet points regarding advantages of Glypressin Solution.

The specific bullet point at issue:

> 'Ready to use for injection (The National Patient Safety Agency recommends that only licensed ready-to-administer or ready-to-use injectable medicines are supplied)'

was referenced to the NPSA patient safety alert, 20 'Promoting safer use of injectable medicines' which stated:

> 'It is preferable that only licensed ready-to-administer or ready-to-use injectable medicines are procured and supplied. The NPSA suggests that NHS organisations should work with the pharmaceutical industry to identify new products and formulations that could make practice safer.'

This NPSA patient safety alert aimed to promote safer use of injectable products. In point 4, paragraph 2, the issue of ready-to-administer or ready-to-use injectables was covered. It was clearly stated that it was preferable to use only licensed ready-to-administer or ready-to-use injectables. This appeared to be a clear recommendation to use such formulations in preference to formulations that required reconstitution prior to use. In the glossary on page 10 'Ready-to-use injectable products' were defined as 'These products require no further dilution or reconstitution before transfer to an administration device. For example, a liquid with an ampoule, of the required concentration, that only needs to be drawn up into a syringe'. Glypressin Solution met these criteria of a ready-to-use injectable product.

The background information, page 6 of the NPSA patient safety alert, discussed and put into context the reasoning behind its recommendations. An ethnographic study on the incidence and severity of intravenous medicine errors in 10 wards of a teaching and non-teaching hospital in the UK, over periods of 6 and 10 days respectively, identified 249 errors. 1% of the errors were potentially serious, 29% were potentially moderate errors and 19% were potentially minor errors. Most errors occurred when giving bolus doses or making up medicines that required multiple step preparation.

Tabulated data in the patient safety alert demonstrated that nearly 24% of medication incidents related to incidents with injectable medicines, of which approximately 73% occurred during administration (which might include preparation) and a further 10% during preparation of medicines in all locations/dispensing in a pharmacy.

Ferring concluded that the NPSA patient safety alert clearly recommended ready-to-use injectable products in preference to those requiring reconstitution prior to use. Ferring also believed that the content of the letter accurately represented the spirit of the NPSA patient safety alert and that there was no exaggeration of the NPSA recommendation, either by including the word 'only' or by its interpretation of the NPSA recommendation 'It is preferable that only licensed ready-to-administer or ready-to-use injectable medicines are procured and supplied' as 'The National Patient Safety Agency recommends that only licensed ready-to-administer or ready-to-use injectable medicines are supplied'.

Ferring therefore did not believe that the claim was in breach of Clauses 7.2 or 7.4.

PANEL RULING

The Panel noted that the NPSA in its patient safety alert, 20 (2007), set out six action points for the NHS and independent sector to promote safer use of injectable medicines. The fourth action point was to 'Implement a "purchase for safety" policy to promote procurement of injectable medicines with inherent safety features'. The further information on that action point stated that the NPSA recommended firstly that policies should advocate the purchase of injectable medicines that included technical information about their preparation and administration and were designed in such a way as

to promote safer practice. This was followed by the advice used as a reference for the material at issue that 'It is preferable that only licensed ready-to-administer or ready-to-use injectable medicines are procured and supplied'. The section then referred to the frequent preparation of an unlicensed injectable medicine from a licensed product and that ready-to-use and ready-to-administer products that could not be prepared in the hospital pharmacy department should be sourced from NHS manufacturing units or commercial 'specials' manufacturers. It was essential that the quality of these medicines was assessed and approved by appropriate quality assurance pharmacists before being purchased. The NPSA patient safety alert included guidance on risk assessment and action plans as well as protocols and procedures for preparing and administering injectable medicines.

The Panel considered that it was clear from the patient safety alert that the NPSA's preference was that only licensed ready-to-administer or ready-to-use injectables were procured and supplied. However, the NPSA accepted that sometimes unlicensed medicines needed to be used or those from NHS manufacturing units or commercial 'specials' manufacturers.

The Panel considered that the 'Dear Pharmacist' letter at issue was not sufficiently clear regarding the NPSA advice. The claim in full read 'Ready to use for injection (The National Patient Safety Agency recommends that only licensed ready-to-administer or ready-to-use injectable medicines are supplied)'. In the Panel's view there was a difference between a preference and a recommendation. Further the claim at issue had been derived from one sentence in four paragraphs of text which referred to 'purchasing for safety' policies. The context of the NPSA statement had not been fully reflected. The letter was misleading and not capable of substantiation in this regard. The Panel ruled breaches of Clauses 7.2 and 7.4.

Complaint received **9 March 2010**

Case completed **15 April 2010**

CASE AUTH/2303/3/10

PROSTRAKAN v FLYNN PHARMA

Promotion of Actiq

ProStrakan complained about an Actiq (oral transmucosal fentanyl citrate) leavepiece and a journal advertisement both issued by Flynn Pharma. Actiq was indicated for the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain.

ProStrakan stated that both pieces referred to pain control and featured the claim 'She needs to turn it on when it starts … and off when it's finished'. 'On' and 'off' were in bold and highlighted in colour ['on' was in green; 'off' was in red].

According to the recent Association for Palliative Medicine guidelines (Davies *et al* 2008), breakthrough pain was characterised by acute onset and short duration (median 30 minutes).

The Actiq summary of product characteristics (SPC) stated that significant analgesia was achieved from 15 minutes following administration. ProStrakan alleged it was therefore inconsistent with the SPC to state or imply that the analgesic effect of Actiq could be 'turned on' when pain started as the SPC stated this would take 15 minutes. Additionally, the SPC stated that T_{max} was around 20 to 40 minutes after consumption of an Actiq unit (range 20 – 480 minutes) and the terminal elimination half-life was about 7 hours. ProStrakan therefore alleged it was misleading to imply that Actiq could be 'turned off' at the end of a breakthrough pain episode that was likely to last only 30 minutes.

ProStrakan was further concerned that the leavepiece featured a photograph of a woman using an Actiq lozenge; she appeared relaxed and not to be in any pain. The Actiq SPC stated that the lozenge should be consumed over a 15 minute period. During this period a patient would not be expected to derive significant analgesia as this took at least 15 minutes to occur. ProStrakan alleged that the image was therefore misleading.

The detailed submission from Flynn is given below.

The Panel disagreed with Flynn's submission that published clinical literature took precedence over the pharmacokinetic data in the SPC. Whatever was in the published literature, product claims must not be inconsistent with the SPC. The Panel also disagreed with Flynn's statement that the claim 'she needs to turn it on when it starts… and off when it's finished' could be regarded as a general statement as to the desirable qualities of a therapy for breakthrough cancer pain. The claim was in promotional material for Actiq and thus inextricably linked to that product.

The Panel noted that Actiq was intended for oromucosal administration. The SPC stated that it should be placed in the mouth against the cheek and moved around using the applicator. The unit was to be consumed over a 15 minute period. During titration if adequate analgesia was not obtained within 15 minutes after the patient completed consumption of a single unit a second one of the same strength could be consumed. Section 5.2 of the SPC stated that T_{max} was around 20 to 40 minutes after consumption of an Actiq unit.

The advertisement and the leavepiece had a photograph of a distressed woman beside which was the claim 'she needs to turn it on when it starts' ('on' was in green and phrase was followed by the picture of a green control button) '… and off when it's finished' ('off' was in red and the phrase was followed by the picture of a red control button). The claim 'Breakthrough Cancer Pain Control' appeared beneath the photograph. The word pain was in red and control was in green.

The Panel considered that the use the pictures of control buttons similar to those found on a television etc implied that the use of 'on' and 'off' in the advertisement ie the switching of pain control on and off with Actiq, was similar to turning an electrical appliance on or off. This was not so. According to the SPC, Actiq produced significantly more breakthrough pain relief compared with placebo at 15, 30, 45 and 60 minutes. Christie *et al* (1998) demonstrated the greatest difference in pain relief in the first 30 minutes which was consistent with the advice given in the SPC regarding the titration of doses. The Panel did not consider that pain control could be turned on and off as implied. When a patient chose to treat their breakthrough pain with Actiq the analgesia would at first increase with time, until pain control was achieved, and then fade with time according to the pharmacokinetics of the medicine. The patient could not turn it on or off at will.

The Panel considered that the claim that pain control could be switched on was inconsistent with the particulars listed in the SPC. The claim that pain control could be switched off was misleading. Breaches of the Code were ruled.

The Panel noted that the front page of the leavepiece featured the black and white photograph of the woman in pain as described above. Three colour photographs on the inside of the leavepiece were clearly of the same woman who appeared relaxed and not in pain. The Actiq

lozenge was not shown in the photographs nor any indication of the time it would take to achieve pain control. The Panel did not consider that the photographs were misleading as alleged; they appeared to show a patient who had been successfully treated with Actiq such that her breakthrough cancer pain was controlled and no longer caused distress. No breach was ruled.

ProStrakan Group plc complained about the promotion of Actiq (oral transmucosal fentanyl citrate) by Flynn Pharma Ltd. The items at issue were an advertisement in the International Journal of Palliative Nursing, December 2009 (ref ACT1709) and a leavepiece (ref ACT0709). It had not been possible to resolve the issues through inter-company dialogue. ProStrakan supplied Abstral (sublingual fentanyl citrate).

Actiq was indicated for the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain.

COMPLAINT

ProStrakan stated that both pieces referred to pain control and featured the claim 'She needs to turn it on when it starts … and off when it's finished'. In both pieces, the words 'on' and 'off' were in bold and highlighted in colour ['on' was in green; 'off' was in red].

According to the recent Association for Palliative Medicine guidelines (Davies *et al* 2008), breakthrough pain was characterised by acute onset and short duration (median 30 minutes). ProStrakan noted that the Actiq summary of product characteristics (SPC) stated that significant analgesia was achieved from 15 minutes following administration. ProStrakan alleged it was therefore inconsistent with the information in the SPC to state or imply that the analgesic effect of Actiq could be 'turned on' when pain started as the SPC stated this would take 15 minutes. ProStrakan alleged a breach of Clause 3.2. Additionally, the Actiq SPC stated that T_{max} was around 20 to 40 minutes after consumption of an Actiq unit (range 20 – 480 minutes) and that the terminal elimination half-life after Actiq administration was about 7 hours. ProStrakan alleged that it was thus misleading to imply that the action of Actiq could be 'turned off' at the end of a breakthrough pain episode that was likely to last only 30 minutes, in breach of Clause 7.2.

ProStrakan was further concerned that the leavepiece featured a photograph of a woman using an Actiq lozenge. The woman appeared relaxed, almost smiling and was reading a magazine; she did not appear to be in any pain. The Actiq SPC stated that the lozenge should be consumed over a 15 minute period. During this period a patient would not be expected to derive significant analgesia as this took at least 15 minutes to occur. ProStrakan alleged that the image was therefore misleading, in breach of Clause 7.8.

RESPONSE

In relation to the alleged breach of Clause 3.2, Flynn noted that ProStrakan was concerned that the claim 'She needs to turn it on when it starts .... and off when it's finished', was in breach of the Code, based on its reading of the Actiq SPC and specifically:

- 'Significant analgesia is achieved **from** (emphasis added) 15 minutes following administration'
- 'Tmax is around 20 to 40 minutes after consumption of an Actiq unit (range 20 – 480 minutes)'
- 'The terminal elimination half-life after Actiq administration is about 7 hours'.

Whilst the second and third statements were accurate quotations from the SPC (Section 5.2), the first was not. The actual statement in the SPC (also Section 5.2) to which ProStrakan referred read as follows:

> 'In patients with chronic cancer pain on stable doses of regularly scheduled opioids to control their persistent pain, Actiq produced significantly more breakthrough pain relief compared with placebo **at** (emphasis added) 15, 30, 45, and 60 minutes following administration.'

To a large extent ProStrakan's interpretation and position turned on its incorrect use and substitution of 'from' in place of 'at'. It was also a further error and misrepresentation of the facts and evidence by ProStrakan when it asserted 'a patient would not be expected to derive significant analgesia as this takes **at least** (emphasis added) 15 minutes to occur'. ProStrakan had thus moved from the facts of 'at 15 minutes' to 'from 15 minutes' and finally to 'at least 15 minutes', and in so doing, materially misrepresented and changed the meaning of the relevant statement in the Actiq SPC. Flynn was particularly concerned that, having drawn ProStrakan's attention to these errors of fact in inter-company correspondence, ProStrakan had ignored the point and repeated an inaccurate and invalid allegation. These matters could surely have been checked and corrected having been highlighted previously to ProStrakan?

Quite simply 'at', 'from' and 'at least' had different meanings and particular relevance to interpretation of the SPC statement in question.

The wording 'at 15 minutes' as included in the SPC meant in or near, within the interval or span of, on, near, or by the time of (15 minutes). In contrast if 'from' was substituted in place of 'of', the meaning of the statement was changed to mean or indicate a separation, differentiation or exclusion, or a specified point as the first of a number of points (from 15 minutes). When the word substitution was taken further to use 'at least' in place of 'at', the statement was altered still further from the original. Thus one now had an interpretation of 'this takes at

least 15 minutes to occur' such that the reader might think that the analgesia occurred at not less than 15 minutes or that the 15 minute time point was the earliest possible time point of importance, magnitude or degree.

In short, the meaning of the cited SPC statement had been materially altered and Flynn found it mischievous of ProStrakan to have done so given Flynn had previously pointed out the errors of fact.

In support of the alleged breach, ProStrakan had also referred to Davies *et al* and specifically the statement that breakthrough pain was characterised by its acute onset and short duration (median 30 minutes). Davies *et al* relied on Portenoy and Hagen (1990) in quoting the median duration of a pain episode as 30 minutes. Portenoy and Hagen and also Davies *et al* went further in reporting the range of duration of a typical pain episode as 1-240 minutes. The median was no more than the middle value in the distribution of durations of pain episodes studied. There would thus be an equal number of pain episodes of less than 30 minutes as there would be episodes of longer than 30 minutes, and they were all included within the range of 1 -240 minutes. This was hardly consistent with ProStrakan's assertion that a breakthrough pain episode was likely to last only 30 minutes. Portenoy and Hagen showed quite clearly that this was not the case. It would follow therefore that an analgesic intervention that lasted only 30 minutes would fail to treat to a greater or lesser extent, up to half of all pain episodes. Based on Portenoy and Hagen (on which Davies *et al* relied), one would ideally wish to have an analgesic intervention that lasted in clinical effect up to 240 minutes to treat all pain episodes.

Actiq had been shown to produce significantly different pain relief at 15 minutes, this time-point being the first one at which the pain intensity difference (PID) and the pain relief (PR) scores were recorded by Christie *et al* (1998) which provided supporting evidence to underpin this statement. Christie *et al* was a supporting reference included in the leavepiece and advertisement. Review of the detail of the paper and specifically Figure 3 provided the evidence. Flynn submitted that it was reasonable to assume that the PID and PR plots had a linear relationship vs time between successive time intervals given that neither variable could be continually measured. Certainly it was more realistic than ProStrakan's position, that given that 15 minutes was the first interval at which PID and PR were measured to the effect or meaning that 'significant analgesia is achieved from 15 minutes'. Equally it was implausible to adopt the view that there was no relief in the period up to 15 minutes and that instant relief was experienced at and beyond 15 minutes. Clearly many patients, if not the majority, would experience increasing pain relief and benefit in the period leading up to 15 minutes.

Another study (Portenoy *et al* 1999) cited in the advertisement, added more weight and evidence in support of Flynn's position. Portenoy reported that 65% of the total pain relief with Actiq occurred within the first 15 minutes. Also in further support and substantiation of the claims set out in the advertisement, Flynn had cited Farrar *et al* (1998). Consistent with the reported findings of Christie *et al*, Farrar *et al* recorded a significant difference between Actiq and placebo in PID and PR scores measured at 15 minutes.

Yet another published study, although not relied on or cited in the material at issue, was an open-label study which evaluated 10 in-patients with breakthrough cancer pain that was not well controlled with their current therapies (Fine *et al* 1991). This study provided experience of 42 Actiq dose administrations and employed a pain questionnaire to provide assessments of pain and relief at 5, 10, 20, 30, 60 and 120 minutes after administration. Onset of analgesia was defined as the time interval between **initiation** (emphasis added) of Actiq administration and notification of pain relief by the patient. Significant and clinically relevant reductions in pain scores were seen at all evaluations from 5 to 120 minutes and the average time of pain relief onset was 9.5 minutes. Indeed, based on the findings of Fine *et al*, it would not be unreasonable to claim meaningful pain relief within ten minutes.

Whilst the previous comments in response to the alleged breach of Clause 3.2 addressed the question of 'turning it on when it starts', they had some relevance to the question of 'turning it off' (when it was finished) which was central to the alleged breach of Clause 7.2.

ProStrakan had postulated that if T_{max} was 20-40 minutes after consumption of an Actiq unit (range 20 – 480 minutes), and that the terminal elimination half-life after Actiq administration was about 7 hours, it was then inconsistent or misleading to imply that the action of Actiq could be 'turned off' at the end of a breakthrough pain episode that was likely to last only 30 minutes.

The data and SPC for Actiq showed that T_{max} typically occurred in 20-40 minutes from the start of dosing, and theoretically 5-25 minutes after onset of the breakthrough cancer pain episode if taken immediately (and accepting that the time to complete administration of a single lozenge was 15 minutes). However Flynn submitted that the published clinical literature, discussed in relation to the alleged breach of Clause 3.2, took precedence over the pharmacokinetic data and better informed readers as to product performance.

Although ProStrakan had commented on the terminal elimination half-life after administration of Actiq, Flynn was unclear as to its relevance to the product claims at issue or the extent if at all, that it supported the alleged breach. Flynn failed to see the significance of metabolism and elimination kinetics to questions around onset of action. It was not the terminal half-life that was important, but the rate of decay from peak levels ie approximately 20

minutes. Side effects were opioid related and dose dependent. The formulation of Actiq (lozenge on a stick) allowed removal of a partially completed dose if the patient experienced side effects. This was an important, unique and differentiating characteristic of the Actiq dose form in the therapy area.

As to the validity of the 'She needs to turn it **on** when it starts…. and **off** when it is finished' strapline, Flynn believed ProStrakan had misrepresented and misinterpreted the Actiq SPC. Flynn agreed that the onset of breakthrough cancer pain was often sudden and its duration could be short (but as Portenoy and Hagen found there was a considerable range or spread in duration). The most effective therapy then was one that had a short duration of onset and an appropriately short duration of action. To that extent, the evidence supported the claims that Actiq would provide analgesia at 15 minutes after initiation of treatment.

Equally, the claim could be regarded as a general statement as to the desirable qualities of a breakthrough cancer pain therapy, rather than a comment which exclusively applied to Actiq. It was the properties of fentanyl itself that were most pertinent to the switching 'off'. Flynn noted that the British National Formulary (BNF) 58 (September 2009) stated that fentanyl was 'particularly useful because it acts within 1-2 minutes and has a short duration of action'. Whilst the speed of onset referred to a systemic route of delivery, once it was inside the body, its subsequent distribution, metabolism and excretion were largely independent of route of administration. Fentanyl was considered a 'short-acting' medicine and was often given as a continuous infusion because of these properties. When the administration was stopped, whether this be discontinuation of an infusion, removal of a partially consumed lozenge, or on completion of a dose, its clinical effects and potential for adverse effects would quickly dissipate. This was the meaning behind 'turning it off when it's finished'. Indeed, Flynn suggested a similar claim might be made of certain other available fentanyl.

Flynn noted that with regard to the alleged breach of Clause 7.8, ProStrakan had taken issue with the picture in the leavepiece of a woman reading a magazine who appeared relaxed, almost smiling and not in pain.

ProStrakan stated correctly from the SPC that the lozenge should be consumed over a 15 minute period. However ProStrakan was wrong to assert that 'During this period a patient would not be expected to derive significant analgesia as this takes at least 15 minutes to occur'. Portenoy *et al* rebutted this position – 65% of the total pain relief with Actiq occurred within the first 15 minutes. Thus it was entirely reasonable and consistent with the data to express a view in imagery or text, suggestive of a patient using Actiq in the licensed way, who experienced meaningful analgesia and pain relief within 15 minutes of initiation of a dose. One could even argue based on Portenoy *et al* that this was the more likely position.

This image showed a patient who had received pain relief and was able to undertake activities in the absence of uncomfortable pain. This was the goal of treatment and the proven benefit of Actiq as evidenced by the literature and a multiyear history of successful use.

In summary, Flynn refuted all three of the breaches alleged. Flynn had set out the facts as to what was and was not included in the SPC, the specific evidence used to support its claims and further literature that added weight to those claims. The majority of patients would experience pain relief before and beyond 15 minutes. The patient images did not include or refer to a timescale – they simply showed a patient not in pain and to a large extent it was irrelevant and hypothetical to debate how long before such a patient had experienced a pain episode and/or taken a dose of Actiq.

PANEL RULING

The Panel noted Flynn's submission that published clinical literature took precedence over the pharmacokinetic data in the SPC. This was not so. Whatever was in the published literature, claims made for a product must not be inconsistent with the particulars listed in the SPC. The Panel also disagreed with Flynn's statement that the claim 'she needs to turn it on when it starts… and off when it's finished' could be regarded as a general statement as to the desirable qualities of a therapy for breakthrough cancer pain. The claim was in promotional material for Actiq and given the context in which it was used it would appear to be inextricably linked to that product.

The Panel noted that Actiq was intended for oromucosal administration. The SPC stated that it should be placed in the mouth against the cheek and moved around using the applicator. The unit should be sucked and was to be consumed over a 15 minute period. The SPC stated that during titration if adequate analgesia was not obtained within 15 minutes after the patient completed consumption of a single unit a second one of the same strength could be consumed.

Section 5.1 of the SPC stated that Actiq produced significantly more breakthrough pain relief compared with placebo at 15, 30, 45 and 60 minutes following administration. Christie *et al* showed that the analgesic effect of Actiq was apparent at 15 minutes and further increased at 30 minutes. Although analgesia had increased again at 60 minutes the efficacy/time curve had begun to flatten out between 30 and 60 minutes. Section 5.2 of the SPC stated that T_{max} was around 20 to 40 minutes after consumption of an Actiq unit.

The advertisement and the leavepiece had a photograph of a distressed woman beside which was the claim 'she needs to turn it on when it starts' ('on' was in green and phrase was followed by the

picture of a green control button) '… and off when it's finished' ('off' was in red and the phrase was followed by the picture of a red control button). The claim 'Breakthrough Cancer Pain Control' appeared beneath the photograph. The word pain was in red and control was in green.

The Panel considered that the use the pictures of control buttons similar to those found on a television or other electrical appliances implied that the use of 'on' and 'off' in the advertisement ie the switching of pain control on and off with Actiq, was similar to turning an electrical appliance on or off. This was not so. According to the SPC, Actiq produced significantly more breakthrough pain relief compared with placebo at 15, 30, 45 and 60 minutes. Christie *et al* demonstrated the greatest difference in pain relief in the first 30 minutes which was consistent with the advice given in the SPC regarding the titration of doses. The Panel did not consider that pain control could be turned on and off as implied. Clearly when a patient chose to treat their breakthrough pain with Actiq the analgesia would at first increase with time, until pain control was achieved, and then fade with time according to the pharmacokinetics of the medicine. The patient could not turn it on or off at will.

The Panel considered that the advertisement and the leavepiece misleadingly implied that pain control with Actiq could be turned on and off instantaneously in a similar way to turning an electrical appliance on and off. The claim that pain control could be switched on was inconsistent with the particulars listed in the SPC. A breach of Clause 3.2 was ruled. The claim that pain control could be switched off was misleading. A breach of Clause 7.2 was ruled.

The Panel noted that the front page of the leavepiece featured the black and white photograph of the woman in pain as described above. The three colour photographs at issue on the inside of the leavepiece were clearly of the same woman who appeared relaxed and not in pain. The Actiq lozenge was not shown in the photographs nor any indication of the time it would take to achieve pain control. The purpose of including the red and green on and off control buttons beneath the photographs was not clear. However the Panel did not consider that the photographs were misleading as alleged; they appeared to show a patient who had been successfully treated with Actiq such that her breakthrough cancer pain was controlled and no longer caused distress. No breach of Clause 7.8 was ruled.

Complaint received **9 March 2010**

Case completed **22 April 2010**

DOCTOR v FOREST

Promotion of Exorex Lotion

A doctor referred to an advertisement for Exorex Lotion (coal tar solution 5% v/w cutaneous emulsion) issued by Forest which featured a photograph of a young woman walking through a supermarket in her underwear; a man looked on open-mouthed. The complainant thought that a sexual element had been introduced into the picture. Whilst this type of advertising might be used for beauty products etc, the complainant did not consider it appropriate for prescription medicines.

The detailed response from Forest is given below.

The Panel considered that the photograph would attract attention however it was relevant to the therapeutic area. The theme of the advertisement was improving the confidence of psoriasis patients. The claim 'Exorex. It has been known to improve confidence.' appeared next to the photograph of the woman. The underwear worn by the woman in the photograph was plain black and not skimpy. Whilst noting the complainant's views, the Panel did not consider that the advertisement failed to meet the requirements of the Code. The advertisement would not offend the majority of the intended audience. No breach of the Code was ruled.

A doctor complained about a journal advertisement for Exorex Lotion (coal tar solution 5% v/w cutaneous emulsion) issued by Forest Laboratories UK Limited.

COMPLAINT

The complainant thought that the advertisement was inappropriate and might not be up to the standards governing the pharmaceutical industry. The advertisement featured a photograph of a young (20-25 year old) woman walking in only her underwear through a supermarket, while a man stood looking at her, open-mouthed. The woman in the advertisement was young/attractive, and being photographed in her underwear, the complainant thought that a sexual element had been introduced into the picture. While this type of advertisement might be used for beauty products etc, the complainant did not think that it was a good thing for prescription medicines.

When writing to Forest, the Authority asked it to respond in relation to Clauses 9.1 and 9.2.

RESPONSE

Forest was surprised to receive this complaint about an advertisement which had run in the medical press for the past six months; the company had put a substantial amount of thought into this advertisement before it was approved for publication, and it believed that it had adhered to the spirit of the Code. In particular, Forest took into account Clause 9 and its supplementary information which proposed that companies should avoid 'the display of naked or partially naked people for the purpose of attracting attention to the material or the use of sexual imagery for that purpose'.

As Exorex Lotion was indicated for the treatment of psoriasis (a common serious dermatological condition that might widely affect the skin), consistent with conventional advertising practice, it was inevitable that partially naked people featured in the material, just as they did in other advertisements for dermatological products. Forest noted that the complainant's attention was drawn equally to the 'open-mouthed man' suggesting that there were multiple points of focus in the advertisement which addressed the issue of self esteem and confidence of people with psoriasis. Forest noted that the use of partially naked people was widespread in the promotion of prescription medicines for dermatological conditions, and a selection of other advertisements was provided. Forest considered that the Exorex advertisement was in line with current industry standards.

The depiction of partially naked people to promote medicines had been ongoing for a long time. Forest noted the advertisements for the breast cancer medicine, Taxotere, which recreated the painting of 'Liberty Leading the People' by Delacroix, and featured a naked breast [Case AUTH/1076/9/00]. Recollection was that it was deemed by the PMCPA that it was in context to show a naked breast in an advertisement for breast cancer, and thus it seemed entirely within the precedent set to show unclothed skin in an advertisement for psoriasis.

The essence of the advertisement at issue was confidence, and the visual conveyed the concept that a psoriasis patient (typically young adults) had responded to therapy and her confidence had increased so much that she wanted to show off her skin to everyone. The advertisement was clearly a light-hearted attempt to summarise a critically important issue for psoriasis sufferers. In the newsletter of the Psoriasis Arthropathy Alliance, Chandler (2005) reported that in a study of 444 psoriasis patients (281 females), 45% of patients reported hiding their psoriatic skin, 58% that their self esteem was affected by the condition and 60% said the disease adversely affected their self confidence. It was noted that normal everyday things could be a challenge, down to the colour of

clothes they wore – would their clothes reveal all the shed skin flakes? Patients with active disease avoided wearing black. Ramsay and O'Regan (1988) reported the results of a survey of the social and psychological effects of psoriasis in 104 patients attending a dermatology clinic. They noted that large numbers of patients avoided swimming and sunbathing because of their psoriasis (72% and 60% respectively) including almost half (46%) of those with mild disease. It was noted that a small percentage (11.5%) avoided leaving their own homes because of psoriasis (making a trip to a supermarket impossible!). It was therefore self evident that an effective psoriasis treatment might improve social wellbeing, including confidence. In a study of Exorex Lotion in mild to moderate psoriasis (Goodfield *et al*, 2003) 38% of patients showed a marked improvement or clearance of their psoriasis after 12 weeks' treatment based on an investigator global assessment of improvement. This well-controlled study supported Forest's advertisement image of healthy looking skin.

Furthermore, Forest considered that the image of the female conveyed that she had found a way of overcoming the social and psychological issues of her disease. Her costume was relatively unrevealing featuring 'big underwear', where no impression of sexual/private parts of the body were seen or implied. All that was on view were areas of the skin that might be seen every day in other contexts (eg a gym, but the advertisement was context loaded.) The clothing was black, underlying the idea that her hair/scalp and torso did not shed flakes. The onlooker was astounded to see that someone had had the confidence to walk through a supermarket, and given the recent press reports of various states of undress by female shoppers in some supermarkets, parodied the news stories.

Forest therefore proposed that the image used in the advertisement was appropriate to convey the ideas of confidence, and that it had not breached Clause 9. It was conventional practice to show partially clothed bodies when promoting dermatologicals, and Forest had taken care to make the advertisement proper for the intended purpose.

PANEL RULING

The Panel noted the requirement of Clause 9.1 of the Code that high standards must be maintained at all times. Clause 9.2 required that materials and activities must recognise the special nature of medicines and the professional standing of the audience and must not be likely to cause offence. The supplementary information to Clauses 9.1 and 9.2 stated that the display of naked or partially naked people for the purpose of attracting attention and the use of sexual imagery for that purpose was unacceptable.

The Panel considered that the photograph used in the advertisement at issue would attract attention however it was relevant to the therapeutic area. The theme of the advertisement was improving the confidence of psoriasis patients. The claim 'Exorex. It has been known to improve confidence.' appeared next to the photograph of the woman. The underwear worn by the woman in the photograph was plain black and not skimpy. Whilst noting the complainant's views, the Panel did not consider that the advertisement failed to meet the requirements of Clauses 9.1 or 9.2 of the Code. The advertisement would not offend the majority of the intended audience. No breach of Clauses 9.1 and 9.2 was ruled.

Complaint received **16 March 2010**

Case completed **13 April 2010**

ANONYMOUS v PFIZER

Alleged sponsorship of a meeting

An anonymous, non-contactable complainant alleged that Pfizer had sponsored a meeting one Saturday morning in March 2010 at a luxury golf and spa resort hotel.

The complainant considered that the location, timing and venue were the factors which persuaded doctors to attend. Pharmaceutical companies should not use such tactics to entice doctors to their meetings. The event lasted only until lunchtime, after which the attendees could use the venue's extensive spa and golf facilities, or go visit local attractions.

The detailed response from Pfizer is given below.

The Panel noted Pfizer's submission that it had had no involvement in the meeting. No evidence had been provided by the complainant to support their allegation. The Panel considered that on the information before it, Pfizer had had no involvement with the meeting and thus no breach of Code was ruled.

An anonymous, non-contactable complainant complained about arrangements for a meeting which the complainant alleged was sponsored by Pfizer Limited.

COMPLAINT

The complainant noted that the meeting at issue had been held on Saturday, 20 March 2010 at a luxury golf and spa resort hotel.

The complainant considered that the location, timing and venue were the factors which persuaded doctors to attend. Pharmaceutical companies should not use such tactics to entice doctors to their meetings. The event lasted only until lunchtime, after which the attendees could use the venue's extensive spa and golf facilities, or visit local attractions.

The complainant considered that if the meeting arrangements were generally known, the public would be appalled.

When writing to Pfizer the Authority asked it to respond in relation to the requirements of Clauses 2, 9.1 and 19.1 of the Code.

RESPONSE

Pfizer submitted that the meeting in question was arranged and organised solely by a third party. Pfizer had no involvement; it neither provided sponsorship and nor did it have a promotional stand at the meeting. No Pfizer personnel attended the meeting. Pfizer provided a letter from the organisers confirming that a meeting had been held that day but that Pfizer was not involved in any way with the meeting.

PANEL RULING

The Panel noted Pfizer's submission that it had had no involvement in the meeting. No evidence had been provided by the complainant to support their allegation. The Panel considered that on the information before it, Pfizer had had no involvement with the meeting and thus it could not be in breach of the Code as alleged. The Panel ruled no breach of Clauses 2, 9.1 and 19.1.

Complaint received **31 March 2010**

Case completed **28 April 2010**

CODE OF PRACTICE REVIEW – MAY 2010

Cases in which a breach of the Code was ruled are indexed in **bold type.**

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2273/10/09	**Lilly v Novo Nordisk**	**Victoza launch**	**Two breaches Clause 3.2 Twenty two breaches Clause 7.2 Eight breaches Clause 7.3 Five breaches Clause 7.4 Two breaches Clause 7.8 Three breaches Clause 7.9 Ten breaches Clause 7.10 Two breaches Clause 8.1 Five breaches Clause 9.1 Four breaches Clause 22.2**	**Appeal by respondent**	**Page 48**
2276/11/09	Anonymous v Roche	Promotion of Xenical	No breach	No appeal	Page 102
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2290/12/09	**Anonymous Clinician v Astellas Pharma**	**Mycamine advisory board**	**Breaches Clauses 2, 9.1, 12.1, 18.1 and 20**	**No appeal**	**Page 126**
2291/1/10	**Hospital Consultant v Flynn**	**Promotion of Actiq**	**Breaches Clauses 7.2 and 7.4**	**Appeal by respondent**	**Page 135**
2293/1/10	**Voluntary Admission by Ferring**	**Pentasa abbreviated advertisement**	**Breaches Clauses 3.2 and 5.6 Two breaches Clause 7.2 Breaches Clauses 7.4, 7.10 and 9.1**	**No appeal**	**Page 141**

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PMCPA | Prescription Medicines Code of Practice Authority

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself. Compliance with the Code is obligatory for ABPI member companies and, in addition, over sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about prescription only medicines made available to the public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend, buy or sell medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the sponsorship of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

It also covers:

- the provision of information to the public either directly or indirectly, including by means of the Internet
- relationships with patient organisations
- the use of consultants
- non-interventional studies of marketed medicines
- grants and donations to institutions.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr William Harbage QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines, or the provision of information to the public, should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY

telephone 020 7747 8880
facsimile 020 7747 8881
by email to: complaints@pmcpa.org.uk.