NUMBER 64 MAY 2009

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 2008

The Annual Report of the Prescription Medicines Code of Practice Authority for 2008 has now been published and copies have been sent to all who are on the mailing list for the Code of Practice Review. Further copies are available on request.

There were 112 complaints in 2008 compared with 127 complaints in 2007. There were 134 complaints in 2006.

The 112 complaints in 2008 gave rise to 103 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, usually because no prima facie case is established.

Of the 280 rulings made by the Code of Practice Panel in 2008, 248 (89%) were accepted by the parties, 23 (8%) were unsuccessfully appealed and 9 (3%) were successfully appealed. This compares with the 4% of rulings which were successfully appealed in 2007.

The Code of Practice Panel met 73 times in 2008 (69 in 2007) and the Code of Practice Appeal Board met 9 times in 2008 (9 in 2007). The Appeal Board considered appeals in 15 cases as compared with 25 in 2007.

The number of complaints made by health professionals in 2008 exceeded the number made by pharmaceutical companies, there being 44 from health professionals and 33 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 and The Pharmaceutical Journal in 2008 in relation to complaints received during the year and the remainder were published in 2009. In relation to complaints received on or after 1 July 2008, one advertisement appeared in the Nursing Standard in 2008 and another was published in 2009.

Copies of the advertisements are on the PMCPA website.

INTER-COMPANY DIALOGUE

Paragraph 5.2 of the Constitution and Procedure states that a complaint will only be accepted by the Authority if the Director is satisfied that the company concerned has previously informed the company alleged to have breached the Code that it proposed to make a formal complaint and offered inter-company dialogue at a senior level in an attempt to resolve the matter, but that this offer was refused or dialogue proved unsuccessful. A formal statement detailing the actions taken must be provided.

It is not unusual in inter-company complaints for the respondent company to claim that the requirements of Paragraph 5.2 have not been met. Parties are reminded that for the process of self-regulation to be efficient, it is important to comply with both the letter and the spirit of the Constitution and Procedure in this regard. Thus complainant companies must be consistent in their citation of clauses of the Code. If inter-company dialogue has been about Clause 7.2, the Authority will not accept a complaint about the same matter which cites Clause 7.10. However, complaints to the Authority do not have to use identical language to that used in inter-company dialogue providing that the formal complaint is not inconsistent with, and does not change the substance of, previous discussions.

Guidance on inter-company dialogue is available on the Authority's website (www.pmcpa.org.uk).

SUPPLY OF EMOLLIENTS FOR PATIENTS TO TRY

From time to time dermatologists ask pharmaceutical companies to provide their hospital departments with packs of emollients so that patients can try out different products to find out which suits them best.

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USE OF EMAIL

The use of email has become familiar to us all to the point where it is widely used for both business and social contact.

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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 dates on which places remain available are:
Monday, 22 June
Monday, 21 September

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.

SUPPLY OF EMOLLIENTS FOR PATIENTS TO TRY

Continued from page 1

Companies often decline such requests because of the limitations on the supply of samples which are set out in Clause 17.

In the Authority's opinion, the supply of emollients in this way does not constitute the supply of samples because a sample is a small supply of a medicine to a health professional so that they can familiarise themselves with it and acquire experience in dealing with it.

That is not the purpose for which dermatologists require packs of emollients and thus they are not samples. They can be provided as free goods if a company so wishes.

USE OF EMAIL

Continued from page 1

Emails are generally regarded as less formal than traditional letters and often casual language is used. Companies should remind staff, however, that if they email a health professional, appropriate administrative staff or others about a matter which relates to their professional role then they should take great care to ensure that the email does not breach the Code through the use of exaggerated claims, immoderate language and the like. A practical rule of thumb might be that if you could not send the message on company headed notepaper, then it should not be sent by email.

The requirements of Clause 9.9 should be kept in mind.

SUBMISSION OF EMAILS

It is not uncommon for companies to submit email correspondence in support of their complaint or response. These emails are often submitted as email trails such that they are presented in reverse chronological order. If several such trails are submitted it can be difficult to determine where one begins and another ends. In addition it is not always obvious who the emails are to and from because only the names, and sometimes only the first names, of the parties appear.

When submitting emails to the Authority it would be helpful if they were submitted in chronological order, in the same way that paper correspondence would be, annotated to clearly show which company or organisation the correspondents represent. It would also be helpful if the correspondents' job titles were included.

EVENT MANAGEMENT COMPANIES AND THE CODE OF PRACTICE

An event management company recently sought general affiliate membership of the ABPI because it believed that this was a prerequisite for gaining business from pharmaceutical companies.

Pharmaceutical companies may well want these companies to be familiar with such things as the requirements of the Code particularly as Clause 16 requires all relevant personnel including third parties to be fully conversant with the Code and relevant laws and regulations. However there is no requirement in the code for supliers including event management companies to become members of the ABPI. Anyone can of course attend PMCPA training courses (details above).

CASE AUTH/2164/9/08

MERCK SHARP & DOHME v TAKEDA

Actos and Competact journal advertisement

Merck Sharp & Dohme complained about a journal advertisement for Actos (pioglitazone) and Competact (pioglitazone and metformin) issued by Takeda.

The advertisement consisted of a stylised illustration of an overweight man, over which was superimposed the headline 'ticktock ticktock ticktock ticktock time to act', in large type. The main text consisted of the claim at issue 'Pioglitazone sustains glycaemic control, but that's not all – in an independent meta-analysis, it has also been shown to reduce ischaemic CV [cardiovascular] events in Type 2 diabetes'. A statement detailing the pioglitazone marketing authorization contra-indications in patients with cardiac failure appeared beneath the product logos. Other than the prescribing information and references, the only other text in the advertisement was the statement 'Pioglitazone is indicated for the treatment of hyperglycaemia in Type 2 diabetes' directly beneath the list of references, in the same type-size as the prescribing information and references.

Actos was indicated as monotherapy, or in combination with other therapy, for glycaemic control in type 2 diabetes.

Merck Sharp & Dohme alleged that the claim at issue promoted pioglitazone outwith the terms of its marketing authorization, was unbalanced, misleading, exaggerated and could not be substantiated.

Merck Sharp & Dohme explained that the major causes of mortality and morbidity in type 2 diabetes were the long-term macrovascular (large-vessel) complications of the disease. The ischaemic risk in type 2 diabetes could be significantly reduced by addressing the hypertension and abnormal lipid profile that frequently accompanied diabetes. Far less clear, however, was whether improving glycaemic control had a beneficial effect on overall ischaemic risk.

In assessing the evidence it was important to distinguish between primary outcome trials (conducted in the general diabetes population irrespective of the presence or absence of pre-existing CV risk) and secondary outcome trials (conducted in patients with a prior history of, or recognised as being at greater risk for, ischaemic heart disease).

Merck Sharp & Dohme discussed data from: the United Kingdom Prospective Diabetes Study (UKPDS): three very large outcome trials in type 2 diabetes (ADVANCE, VADT and ACCORD) presented at the American Diabetes Association meeting which examined a variety of treatment strategies, and Takeda's own secondary outcome trial with pioglitazone (PROactive).

Merck Sharp & Dohme noted the following, which were relevant to subsequent arguments:

1 **The claim of a reduction in ischaemic events with pioglitazone was the primary claim and the main, if not the sole, purpose of the advertisement was to place the ischaemic events claim in front of prescribers.**

2 **The whole tenor of the advertisement (the 'ticking clock' theme, the wording 'time to act') implied urgency, that use of pioglitazone might prevent adverse consequences of diabetes and further implied that pioglitazone could reduce the mortality and morbidity attributable to these complications.**

3 **The claim was all-embracing. There was no differentiation between different classes of patients, particularly those with and without increased CV risk and thus it was implied that pioglitazone reduced ischaemic events in the general diabetes population. Substantiation of such an all-embracing claim required robust primary outcome data, or its equivalent.**

4 **The claim was referenced solely to Lincoff *et al* (2007), a meta-analysis described as 'independent' in the advertisement.**

5 **The only description of the licence indications for pioglitazone, other than in the prescribing information, was in the small-font statement below the references.**

Pioglitazone was not licensed to reduce ischaemic events in type 2 diabetes nor mentioned in any section of the summary of product characteristics (SPC).

The advertisement referred to the meta-analysis as 'independent' although Takeda had provided the data for the meta-analysis together with a grant to support the statistical analyses. Whether or not the company had any input into the design or conclusions of the analysis, readers would not conclude from the word 'independent' that the sole financial support for the meta-analysis had been provided by the company whose medicine was under investigation. Merck Sharp & Dohme therefore believed this statement to be misleading.

The detailed response from Takeda is given below.

The Panel noted that Actos was licensed for glycaemic control in type 2 diabetes. There was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition.

The advertisement featured the outline of an overweight man and running the two pages, and across the man's chest was the statement 'ticktock ticktock ticktock ticktock time to act'. The spacing between successive ticktocks appeared to decrease as if to suggest a clock speeding up with 'time to act' appearing as an alarm call. The Panel considered that some readers would associate the 'ticktock' phrase, particularly given its positioning over the man's chest, with the heart ie 'ticker'. In that regard the Panel considered that the most prominent visual and text of the advertisement suggested cardiovascular issues as opposed to the importance of glycaemic control.

The claim, which ran down the right-hand side of the advertisement, was one continuous statement: 'Pioglitazone sustains glycaemic control but that's not all – in an independent meta-analysis, it has also been shown to reduce ischaemic CV events in Type 2 diabetes'. In that regard the Panel considered that Takeda's description of two claims ('Pioglitazone sustains glycaemic control' followed by a secondary, discursive claim 'shown to reduce ischaemic CV events') with the wording of the second being significantly less prominent than the 'primary claim' was misleading and disingenuous. In the Panel's view the use of the phrase 'but that's not all' suggested that both actions of pioglitazone (glycaemic control and reduction in ischaemic CV events) were of equal importance; some readers would assume that pioglitazone was licensed for both which was not so.

The Panel considered that the claim at issue promoted pioglitazone outwith the terms of its marketing authorization as alleged. The reduction in ischaemic CV events had not been sufficiently clearly placed in the context of being a benefit of glycaemic control. In the Panel's view, given the limited amount of time that people might spend reading a journal advertisement, it was not unreasonable to assume that most readers would read the claim as one simple statement that pioglitazone could be used for glycaemic control and to reduce CV events. A breach of the Code was ruled. On appeal by Takeda the Panel's ruling was upheld by the Appeal Board.

The Panel noted that much of the pioglitazone data in Lincoff *et al* was derived from PROactive which had suggested that treatment was beneficial from the cardiovascular standpoint although significant differences were not observed in the pre-specified primary endpoint (death, myocardial infarction, stroke, acute coronary syndrome, leg amputation or coronary or leg revascularization). Lincoff *et al* stated that their results constituted reasonably strong evidence that pioglitazone reduced the risk of cardiovascular ischaemic endpoints in type 2 diabetes. The Panel noted, however, that the claim at issue, '[pioglitazone] has also been shown to reduce ischaemic CV events in Type 2 diabetes', went further than Lincoff *et al*. The Panel considered that Lincoff *et al* did not substantiate the robust unqualified claim at issue. The claim was misleading in that regard. Breaches of the Code were ruled. On appeal by Takeda the Appeal Board considered that the particular claim regarding the reduction of CV events could be substantiated by Lincoff *et al* and no breach of the Code was ruled.

The Panel noted that the claim referred to Lincoff *et al* as being an independent analysis. At the end of the published paper the authors had acknowledged financial support from Takeda and stated that the company had been involved in the collection of data for the original trials used in the meta-analysis and participated in the identification of adverse events from records within its database. Takeda had provided the database of eligible trials but did not participate in the statistical analyses used for the paper. The company was not involved in preparing the manuscript and was not permitted to review or comment on the content. In the Panel's view Takeda had thus had some involvement in Lincoff *et al* albeit involvement that would not have affected the outcome. Nonetheless the Panel did not consider that describing Lincoff *et al* as independent, in an advertisement, gave the right impression. It implied that Lincoff *et al* was wholly independent of Takeda which was not so. The Panel thus considered that the phrase 'independent analysis', in the context in which it occurred, was misleading as alleged. A breach was ruled which was upheld on appeal by Takeda, the Appeal Board noting that those reading the advertisement would not have the benefit of the declaration of financial support given in the published paper.

Merck Sharp & Dohme Limited complained about a two page journal advertisement (ref AB080313) for Actos (pioglitazone) and Competact (pioglitazone and metformin) issued by Takeda UK Limited which had appeared in Pulse. Inter-company dialogue had failed to resolve the matter.

The advertisement consisted of a stylised illustration of an overweight man, over which was superimposed the headline 'ticktock ticktock ticktock ticktock time to act', in large type. The main text consisted of the claim at issue 'Pioglitazone sustains glycaemic control, but that's not all – in an independent meta-analysis, it has also been shown to reduce ischaemic CV [cardiovascular] events in Type 2 diabetes'. A statement detailing the pioglitazone marketing authorization contra-indications in patients with cardiac failure appeared beneath the product logos. Other than the prescribing information and references, the only other text in the advertisement was the statement 'Pioglitazone is indicated for the treatment of hyperglycaemia in Type 2 diabetes' directly beneath the list of references, in the same type-size as the

prescribing information and references.

Actos was indicated in the treatment of type 2 diabetes mellitus as monotherapy in patients inadequately controlled by diet and exercise for whom metformin was inappropriate due to contraindications or intolerance. It could be used as dual therapy or triple therapy in patients on certain regimes including those with insufficient glycaemic control. Actos could also be used in combination with insulin in type 2 patients with insufficient glycaemic control on insulin for whom metformin was inappropriate due to contraindications or intolerance.

COMPLAINT

Merck Sharp & Dohme alleged that the claim at issue promoted pioglitazone outwith the terms of its marketing authorization, in breach of Clause 3.2, was unbalanced, misleading and exaggerated in breach of Clause 7.2, and could not be substantiated in breach of Clause 7.4.

Merck Sharp & Dohme explained that the major causes of mortality and morbidity in type 2 diabetes were the long-term macrovascular (large-vessel) complications of the disease. These resulted from ischaemic atherosclerotic events, particularly angina, myocardial infarction and stroke. The risk of developing these events was massively increased in type 2 diabetes relative to the general population. It was generally accepted, that the ischaemic risk in type 2 diabetes could be significantly reduced by addressing the hypertension and abnormal lipid profile that frequently accompanied diabetes.

Far less clear, however, was whether improving glycaemic control (ie reducing blood glucose *per se*) had a beneficial effect on overall ischaemic risk. Partly, this was because it was difficult to generate the evidence, as CV outcome trials in type 2 diabetes required large numbers of patients evaluated over many years, and it was often problematic to disentangle the possible contribution of improved glycaemic control from that derived from confounding factors.

In assessing the available evidence, it was important to distinguish between primary outcome trials, ie those conducted in the general diabetes population irrespective of the presence or absence of pre-existing CV risk and secondary outcome trials, ie those conducted in patients with a prior history of, or recognised as being at greater risk for, ischaemic heart disease.

The only primary outcome trial to show any ischaemic heart disease event benefit with an antidiabetic agent was the United Kingdom Prospective Diabetes Study (UKPDS), published over a decade ago. Even here, the improvements in ischaemic heart disease risk were only seen in the subgroup of obese patients treated with metformin (patients treated with other antidiabetic medicines did not show any significant CV outcome benefit). This single finding ensured that metformin was universally recognised in national and international guidelines as the treatment of first choice in type 2 diabetes.

In 2008, three very large outcome trials in type 2 diabetes (ADVANCE, VADT and ACCORD) were presented at the American Diabetes Association meeting. These trials examined a variety of treatment strategies, comparing, as did the UKPDS, intensive vs standard glucose control, but were unable to demonstrate any significant reduction in CV risk with more rigorous blood glucose control.

Takeda's own secondary outcome trial with pioglitazone (PROactive) would be discussed below. However, it should be clear from the above that a claim of a general reduction of ischaemic CV events with an antidiabetic agent would carry extraordinary significance, in effect representing the 'holy grail' of diabetes claims. Were such a claim to be justified and substantiated, it would potentially afford major competitive advantage to the agent concerned. Merck Sharp & Dohme primarily contended that the claim in the advertisement was neither substantiated by the available evidence, nor (even if it were substantiable) justified on the basis of the current pioglitazone marketing authorization.

Merck Sharp & Dohme noted that the following were relevant to subsequent arguments:

1 The claim of a reduction in ischaemic events with pioglitazone was the primary claim made in the advertisement. Of eight lines of text, only two were concerned with glycaemic control, the remainder with ischaemic events. In Merck Sharp & Dohme's opinion, it was clear that the main, if not the sole, purpose of the advertisement was to place the ischaemic events claim in front of prescribers.

2 The whole tenor of the advertisement (the 'ticking clock' theme, the wording 'time to act') implied urgency, that use of pioglitazone might prevent adverse consequences of diabetes. Given point 1, above, this could only mean ischaemic CV consequences, further implying that pioglitazone could reduce the mortality and morbidity attributable to these complications.

3 The claim was all-embracing. No differentiation was made between different classes of patients, particularly those with and without increased CV risk. The reader would inevitably assume that pioglitazone had been shown to reduce ischaemic events in the general diabetes population. Substantiation of such an all-embracing claim would require a primary outcome trial, or its equivalent in terms of robust evidence.

4 The claim was referenced to a single source: Lincoff *et al* (2007), a meta-analysis published in the Journal of the American Medical Association.

5 The meta-analysis was described as 'independent' in the advertisement.

6 The only description of the licence indications for pioglitazone, other than in the prescribing information, was in the small-font statement immediately below the references.

Merck Sharp & Dohme submitted that pioglitazone was not licensed to reduce ischaemic events in type 2 diabetes. Such an effect was neither included in the main indications for pioglitazone, nor in any section of the current summary of product characteristics (SPC), including that on additional pharmacodynamic effects.

In inter-company dialogue, Takeda stated that the PROactive trial, the main component of Lincoff *et al*, had been reviewed by the European licensing authority, and was mentioned in the pioglitazone licence. Leaving aside the fact that the claim was referenced to the meta-analysis as a whole, rather than solely to its PROactive component, examination of the pioglitazone licence revealed that, other than summarising the design of the PROactive trial, the sole licence wording referring to it was as follows:

'Although the study failed regarding its primary endpoint, which was a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, major leg amputation, coronary revascularisation and leg revascularisation, the results suggest that there are no long-term cardiovascular concerns regarding use of pioglitazone. However, the incidences of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.'

The licensing authority thus undertook a full review of the principal study included in Lincoff *et al* and – while deriving some reassurance concerning the cardiac safety of pioglitazone – did not see fit to include any comment on the effect of pioglitazone on ischaemic event rate other than to state that the study failed its primary endpoint. The inescapable conclusion was that the authority did not view the PROactive results as warranting mention of the CV effects of pioglitazone, even in the high-risk group of patients evaluated, let alone the general diabetes population.

Furthermore, Lincoff *et al* stated in the final paragraph of their publication:

'In conclusion, the findings of this meta-analysis provide evidence of a favorable effect of pioglitazone on ischaemic vascular complications, **which is distinct from the efficacy of thiazolidinediones in reducing blood glucose levels'** [emphasis added].

However, even assuming this to be true, pioglitazone was not licensed for such extra-glycaemic effects. This was recognised in the advertisement by the inclusion of the statement 'Pioglitazone is indicated for the treatment of hyperglycaemia in Type 2 diabetes' under the references.

In summary, even if the claimed reduction in ischaemic events could be appropriately substantiated (which Merck Sharp & Dohme did not believe to be the case), appropriate regulatory scrutiny and amendment of the pioglitazone licence would be necessary before a general promotional claim along these lines could be used. The claim was significant, high-level and all-embracing, and was given clear emphasis above any other claim in the advertisement. As such, it could not be considered as an ancillary effect of the medicine, but as an entirely new indication.

Accordingly, Merck Sharp & Dohme believed that Takeda's promotional use of the claim that pioglitazone reduced ischaemic CV events in type 2 diabetes was not in accordance with the terms of its marketing authorization, in breach of Clause 3.2.

Turning to Lincoff *et al*, Merck Sharp & Dohme did not believe that the data supported a broad and all-embracing claim of ischaemic CV event reduction.

Lincoff *et al* incorporated results from 19 studies the largest of which was PROactive (approximately one-third of all pioglitazone-treated patients). This was also the only study specifically designed to assess CV event rates. Despite the fact that the advertisement was referenced to the meta-analysis as a whole, in inter-company dialogue Takeda emphasised the results from PROactive. Accordingly, Merck Sharp & Dohme began with PROactive and widened the argument out to include the whole meta-analysis. For clarity, Merck Sharp & Dohme had numbered the essential points:

1 PROactive was specifically designed to evaluate the effects of pioglitazone on ischaemic CV events in high-risk patients, ie those with a prior history of CV disease. As such, any results from it, positive or otherwise, could only be applied to that subset of patients, and not to the whole diabetes population.

2 The primary endpoint of the study, a composite of ischaemic CV events and vascular interventions, failed to reach statistical significance. Although some of the subsequent analyses of the secondary endpoints proved to be significant, these findings could only be considered as indicative, rather than definitive.

3 As noted above, the European licensing authority examined all of the data pertaining to PROactive, and, while the results provided some reassurance about the long-term cardiac safety of pioglitazone, the authority evidently did not find the ischaemic event data sufficiently compelling to include them in the pioglitazone licence, even as an additional effect. Indeed, the only comment

it made on the CV event results was that the trial failed to reach its primary endpoint.

4 This lack of data, combined with the regulatory issues, prevented PROactive being used to underpin a general promotional claim in the UK that pioglitazone reduced ischaemic CV event rates in high-risk patients with type 2 diabetes (let alone in diabetics generally).

5 Takeda had implicitly recognised this by not, to Merck Sharp & Dohme's knowledge, using PROactive in this way in any UK promotional materials.

6 Takeda's assertion in inter-company dialogue that Lincoff *et al* 'extends' the findings of PROactive to the general diabetic population was thus disingenuous, as there was no usable claim in high-risk patients to be extended in the first place.

7 Merck Sharp & Dohme noted that PROactive accounted for over 30% of the patients in Lincoff *et al*. Although it was evidently impossible for Merck Sharp & Dohme to perform a full sensitivity analysis on the meta-analysis, it seemed highly probable that PROactive therefore contributed the great majority of the 'positive' data. This was particularly likely as the primary endpoint chosen for Lincoff *et al* was not the composite used as the (failed) primary endpoint in PROactive, but rather one of the secondary PROactive endpoints that did reach significance. As such, majority evidence from a secondary outcome study was being used improperly to support a primary claim.

8 None of the other 18 studies included in Lincoff *et al* were designed or powered to be primary or secondary CV outcome studies. Nine lasted less than 12 months which was an extremely short time to look for CV endpoints, given that the UKPDS took over 10 years to complete. Furthermore, six of the studies included fewer than 200 pioglitazone-treated patients. It was inconceivable that, taken separately or together, these studies could form the basis of any reasonable claim of ischaemic CV event reduction.

9 Takeda sought to make a general, all-embracing claim of ischaemic event reduction with pioglitazone solely based on a single meta-analysis which included, as its main component, a trial which failed to conclusively demonstrate a reduction in high-risk patients, combined with a number of additional trials, none of which were designed to demonstrate this outcome, and many of which were totally unsuitable for this purpose.

In summary, Merck Sharp & Dohme believed that claims of such all-embracing significance required appropriate substantiation; Lincoff *et al* did not represent such evidence. Indeed, the authors acknowledged that the meta-analysis had 'important limitations'. Merck Sharp & Dohme contended that Lincoff *et al* was, at best, hypothesis-generating, and that its preliminary findings would need to be backed up by properly designed randomised controlled trials (and appropriately licensed) before they could support a claim of this kind.

For these reasons, Merck Sharp & Dohme believed that the claim at issue was not capable of appropriate substantiation and that it was thus neither balanced nor fair. Merck Sharp & Dohme alleged breaches of Clauses 7.2 and 7.4.

Merck Sharp & Dohme noted that in the advertisement, the meta-analysis was referred to as 'independent'. However, the paper itself acknowledged that Takeda had provided the data for the meta-analysis together with a grant to support the statistical analyses. Whether or not the company itself had any input into the design or conclusions of the analysis, Merck Sharp & Dohme believed that the readers would not conclude from the word 'independent' that the sole financial support for the meta-analysis had been provided by the company whose medicine was under investigation. Merck Sharp & Dohme therefore believed this statement to be misleading, in breach of Clause 7.2.

In conclusion Merck Sharp & Dohme stated that given the broad significance and misleading nature of the claim at issue, which had been used for several months, the Panel should consider referring this matter to the ABPI Board of Management, with a view to requiring Takeda to issue a formal retraction.

RESPONSE

Takeda did not accept that the reference in the advertisement to the results of an independent meta-analysis were out of context and off balance with the licensed indications for pioglitazone. In view of the overall style and presentation of the different elements of the advertisement, Takeda did not consider that prescribers were likely to regard the main emphasis as being upon ischaemic CV risk reduction nor were likely to be misled into thinking that CV event reduction was claimed as a licensed indication.

The advertisement clearly emphasised the need for, and importance of, glycaemic control in the treatment of type 2 diabetes. The dominant image of a man in the advertisement portrayed a typical person with uncontrolled type 2 diabetes – it did not emphasise or focus upon ischaemic CV risk. Prescribers would immediately recognise that central abdominal obesity in diabetic patients indicated a need for glycaemic control and this was reflected in the advertisement's superscript ('tick tock tick tock … time to act') which provided a 'call to action' in this regard. Therefore, Takeda

considered that the most prominent visual and textual messages before prescribers were those which highlighted the importance of tight glycaemic control in type 2 diabetes. The text at issue, 'reduce ischaemic CV events' was the fourth element in the advertisement – after the visual of the man, the superscript wording of 'tick tock tick tock … time to act', and the primary claim of 'Pioglitazone sustains glycaemic control'. The wording 'reduce ischaemic CV events' was significantly less prominent than either the image of the man, the primary claim and/or the superscript and was explicitly attributed to a meta-analysis, thus making it clear the statement solely presented data from this recent meta-analysis.

Although pioglitazone was not specifically licensed for ischaemic CV event reduction, Takeda noted that the use of CV outcome claims were permitted in promotional material where these were set in the context of the licensed indication (Case AUTH/1340/7/02) and Takeda considered the layout and content of the present advertisement to be consistent with that ruling.

Furthermore, the Medicines and Healthcare products Regulatory Agency (MHRA) in previous dialogue had specifically permitted Takeda to use data from Lincoff *et al* in promotional material, as long as the claim was set in context of any safety concerns. The Authority had previously also ruled to permit claims on ischaemic CV outcomes based upon the PROactive study (Case AUTH/2011/6/07).

The data from Lincoff *et al* was representative of the current evidence base for pioglitazone, and did not conflict with the current evidence base for the management of type 2 diabetes.

Taking all these points into account, as well as the detailed response provided below in part 2, Takeda strongly refuted the allegations that the advertisement breached the Code and/or specifically any of the Clauses 3.2, 7.2 and 7.4.

Takeda noted that Merck Sharp & Dohme had three main concerns, namely that the advertisement promoted pioglitazone outwith the terms of its marketing authorization (alleged breach of Clause 3.2), that the claim at issue was unbalanced, misleading and exaggerated (alleged breach of Clause 7.2) and could not be substantiated (alleged breach of Clause 7.4).

- Alleged breach of Clause 3.2

The advertisement was structured so as to present (visually and textually) the importance of glycaemic control treatment in type 2 diabetes. The text summarised, in an accurate, balanced, fair and objective manner, the licensed indication of sustained glycaemic control with pioglitazone treatment and the result of a recent meta-analysis of pioglitazone data (Lincoff *et al*) so as to enable health professionals to form their own opinions as to the therapeutic value of using the medicine in type 2 diabetics. Taking into account the contraindication for heart failure and the reference to ischaemic CV risk reduction, the advertisement also referred explicitly to this contraindication, drawing prescribers' attention to the necessity for ongoing monitoring of patients, with a view to promoting the rational use of the medicine. Takeda again referred to the rulings made in Cases AUTH/1340/7/02 and AUTH/2011/6/07.

Takeda had recently discussed and agreed the use of ischaemic CV claims, based on Lincoff *et al* and the PROactive data with the MHRA. Takeda gave details of the MHRA's response which were confidential.

The main impact of the advertisement was via the stylised outline of a man and the repeated 'ticktock time to act' superscript. However, the advertisement also contained two less prominent textual claims. The primary claim 'Pioglitazone sustains glycaemic control' based on the licensed indication of pioglitazone. The following, secondary discursive claim 'shown to reduce ischaemic CV events' was explicitly attributed to an identified, independent meta-analysis, making it clear that it was not asserted as a formally licensed indication but was rather based solely upon meta-analysis data. The reference to 'Type 2 diabetes' following the two claims meant that the secondary claim was set explicitly in the context of the management of hyperglycaemia in type 2 diabetics, ie within the licensed indication of pioglitazone.

Merck Sharp & Dohme's central complaint appeared to be that the reference to Lincoff *et al* was not in accordance with the licensed indications for pioglitazone. Takeda disagreed; the main emphasis of the advertisement was clearly upon the need for, and importance of, glycaemic control in type 2 diabetics. The large, stylised image of a man, clearly exhibiting central abdominal obesity, characteristic and typical of a patient with type 2 diabetes, dominated the advertisement. This image therefore immediately portrayed a person whose diabetes was out of control and who needed glycaemic control. The superscript 'ticktock time to act' communicated a 'call to action' to the reader. Therefore, the most prominent visual and textual messages before prescribers clearly highlighted the importance of glycaemic control in type 2 diabetics.

The third level claim at issue was of course significantly less prominent than either the graphic image of the man and/or the superscript. However, the manner of presentation was very different in relation to the other textual claims used in the advertisement. Contrasting language was employed with the licensed indication being clearly stated first and also directly (ie without any attribution): 'pioglitazone sustains glycaemic control' and only after that (effectively as the fourth element in the advertisement), the more discursive follow-on claim: 'in an independent meta-analysis, it has been shown to reduce ischaemic CV events'. The latter was clearly not a primary claim as it started with an

explicit attribution as to its source, which further differentiated these two claims in terms of their impact on prescribers. In view of the overall style and presentation of the different constituent elements of the advertisement, prescribers were neither likely to regard the advertisement's main emphasis as being upon ischaemic CV risk reduction nor to be misled into thinking that the CV event reduction claim was a licensed indication.

Takeda submitted that the patients included within the meta-analysis represented a wide variety of type 2 diabetics, including those with and without established vascular disease, and thus represented a real life type 2 diabetes population. Lincoff *et al* contained a significant proportion of patients from PROactive, ie those at high cardiovascular risk with evidence of previous macrovascular disease. The authors stated that the findings of the meta-analysis 'extend the observations of PROactive in **a larger population and to lower-risk patients without established vascular disease**' (Takeda's emphasis). Tests for heterogeneity performed by Lincoff *et al* showed no difference between shorter and longer term studies, among trials of patients with or without established vascular disease, or importantly, PROactive and all other trials pooled together. Therefore the reference to the conclusions of the meta-analysis in the advertisement did not require any qualification as to patient population.

- Alleged breach of Clause 7.4

The secondary claim in the advertisement *de facto* referred to the primary results of Lincoff *et al*, which was appropriately referenced; as such it was implicit that the claim was substantiated by Lincoff *et al*.

Takeda noted that in Lincoff *et al*, the primary composite end point of death, nonfatal myocardial infarction, or nonfatal stroke occurred in significantly fewer patients on pioglitazone than control (HR, 0.82; 95% CI, 0.72 – 0.94; p=0.005). The authors stated that the primary composite endpoint 'represents irreversible ischemic events and is widely used for cardiovascular outcome trials of chronic therapies' and that 'the current meta-analysis of data from the pioglitazone database presented here constitutes reasonably strong evidence that this agent does, in fact, reduce the risk of cardiovascular ischemic endpoints among patients with Type 2 diabetes mellitus'.

Nineteen trials enrolling 16,390 patients were analysed in the meta-analysis, with pioglitazone treatment lasting from 4 months to 3.5 years. The meta-analysis included patients with uncontrolled type 2 diabetes ie those within the licensed indication. The methods section of Lincoff *et al* clearly explained the type of patients included within the meta-analysis stating 'In general, studies included adult patients with Type 2 diabetes mellitus and inadequate glycemic control. The primary objective of most of the trials was to determine the efficacy of pioglitazone, in combination or comparison with insulin, metformin, sulfonylureas, or rosiglitazone in improving glycemic control'. The studies included in the meta-analysis were therefore fully aligned with the licensed indication for pioglitazone.

Lincoff *et al*, conducted thorough sensitivity analyses, testing for heterogeneity within the studies included to show that the results did not differ with differing variables.

The hierarchy of evidence ranked systemic reviews and meta-analysis as the highest level of evidence. The National Institute for Health and Clinical Excellence (NICE) ranked meta-analysis data as class 1, ie the highest level of evidence. In a guide to interpreting meta-analyses, Davies and Crombie stated: 'The validity of the meta-analysis depends on the quality of the systematic review on which it is based, using both published and unpublished data and where possible using time to first event' and 'Good meta-analyses allow for complete coverage of all relevant studies and look for the presence of heterogeneity and can explore the robustness of the main findings using sensitivity analysis', as was the case for the meta-analysis by Lincoff *et al*.

The European Medicines Evaluation Agency's (EMEA's) guidance stated: 'valuable information has been provided by pooling data from several studies. In the biostatistical guidelines from ICH E9, meta-analytic techniques are recognised as a useful tool to summarise the overall efficacy results of a drug application and to analyse less frequent outcomes in the overall safety evaluation'.

There were a number of accepted regulatory purposes for meta-analysis, including, but not limited to, evaluation of an additional efficacy outcome that required more power than the individual trials could provide.

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) also ranked meta-analysis data highly, having recently updated their joint consensus statement on the management of hyperglycaemia in type 2 diabetes, within which they incorporated Lincoff *et al* to state 'a meta-analysis of the clinical trial data regarding cardiovascular disease risk and pioglitazone has suggested that the drug exerts a protective effect'.

Indeed, recently the EMEA had incorporated the results of meta-analysis conducted by both the manufacturing company (GlaxoSmithKline) as well as the same group as Lincoff *et al* (the Cleveland Clinic, US) to the prescribing information for rosiglitazone-based products to state 'The available data indicate that treatment with rosiglitazone may be associated with an increased risk of myocardial ischaemic events'. These data reported for rosiglitazone had also led to the inclusion of a contra-indication for use in acute coronary syndrome and warnings for use in ischaemic heart

disease and peripheral arterial disease.

The Food and Drugs Administration had also similarly amended its prescribing information with this meta-analysis data, adding an additional black box warning stating 'A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total Patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with an increased risk of myocardial ischaemic events such as angina or myocardial infarction'.

Taking all of these points into account, Takeda therefore refuted the allegation of breach of Clause 7.4.

- Alleged breach of Clause 7.2

It was widely accepted that reducing HbA1c (ie the most commonly used and recommended measurement for glycaemic control) was associated with improved ischaemic cardiovascular outcomes. The UKPDS study (UKPDS 35) associated HbA1c reduction with improved cardiovascular outcomes. The study showed every 1% reduction in HbA1c proffered relative risk reductions of 21% for any end point related to diabetes (95% confidence interval 17% to 24%, $p < 0.0001$), 21% for deaths related to diabetes (15% to 27%, $p < 0.0001$), 14% for myocardial infarction (8% to 21%, $p < 0.0001$).

NICE, which could be regarded as representing the body of UK scientific opinion, in its recently updated guidance for the management of type 2 diabetes, evaluated the available data for the relationship between HbA1c and microvascular and/or macrovascular complications and supported the notion that HbA1c reduction was linked to effects on cardiovascular outcomes; it stated: 'Cardiovascular risk can be reduced by 10-15% per 1.0% reduction of HbA1c, the treatment effect and epidemiological analysis of UKPDS giving the same conclusion'.

NICE had also evaluated the Lincoff *et al*, data and stated: 'A meta-analysis of 19 pioglitazone trials (with the PROactive study being the largest study included) reported that treatment with pioglitazone was associated with a significantly lower risk of death, MI, or stroke. Pioglitazone was also associated with a significantly higher risk of serious heart failure'.

Merck Sharp & Dohme's reference to ADVANCE, ACCORD and VADT (not yet published, presented at ADA 68th Scientific Sessions, June 2008) was misleading as these studies did not relate to either pioglitazone or to any of the other studies included in Lincoff *et al* (since none of the studies included in Lincoff *et al* investigated intensive control of glycaemia in type 2 diabetes).

None of the studies identified by Merck Sharp & Dohme were designed to investigate the impact of pioglitazone on cardiovascular disease and therefore the results of these studies were not related to the relevant body of evidence demonstrating the effect that pioglitazone had on ischaemic cardiovascular effects. In particular, Takeda noted:

- VADT did not evaluate pioglitazone usage (only rosiglitazone) and was yet to be published;
- there was only limited pioglitazone usage in ACCORD (90% rosiglitazone use in the intensive arm with only a small proportion using pioglitazone);
- in ADVANCE, the exact pioglitazone usage was not defined though there was only 17% thiazolidinedione use in the intensive arm;
- all of these trials were designed to evaluate intensive vs standard/conventional glycaemic control on a composite of CV outcomes (VADT, ACCORD) or micro-and macrovascular outcomes (ADVANCE) and were not designed to evaluate the effects of any particular therapy;
- the target HbA1c in these trials was much lower than in normal clinical practice and in general the control arms had HbA1c levels closer to those reached in the UK. Thus the treatment arms did not reflect standard UK clinical practice.

In view of the above, Takeda did not consider that the studies identified by Merck Sharp & Dohme undermined or contradicted Lincoff *et al*.

The evidence base for the effects of pioglitazone on ischaemic CV outcomes included Lincoff *et al* as well as PROactive. It was therefore not correct to state that the secondary claim in the advertisement was not appropriately substantiated by current scientific data.

Lincoff *et al* had previously been discussed above.

The primary endpoint for PROactive, which proffered a non-significant reduction with pioglitazone treatment, evaluated a reduction in macrovascular events, including both ischaemic (eg myocardial infarction, stroke) and peripheral (eg amputation, peripheral revascularisation) events. However, the main secondary endpoint and further subsequent analyses of PROactive were specific to ischaemic events, for example, the main secondary endpoint of PROactive evaluated time to the composite of all-cause mortality, myocardial infarction (excluding silent myocardial infarction) and stroke – the same composite evaluated by Lincoff *et al* as the primary endpoint in the meta-analysis showed a significant relative risk reduction for this composite endpoint; with a 16% significant relative risk reduction (2.1% absolute risk reduction) shown in PROactive and an 18% significant relative risk reduction (1.3% absolute risk reduction) in Lincoff *et al*.

Importantly, the European Public Assessment Report (EPAR) published by the EMEA (January

2007), which underlaid the subsequent reference to PROactive in the SPC, explicitly supported the suggestion that there was a trend towards ischaemic benefit seen in the PROactive study. For example, the EPAR stated:

'Results of the analysis of the main secondary composite end point, a composite of 3 disease end points of the primary end points of the primary end point (ie all cause mortality, non fatal MI (excluding silent MI) and stroke **showed a statistically significant 16% relative risk reduction of the events within the composite with the pioglitazone treatment**. The COX proportional hazards model gave an estimate of 0.84 (95% CI:0.72, 0.98; P=0.0277) for the hazard ratio comparing pioglitazone with placebo' (Takeda's emphasis).

Takeda noted that promotional claims based upon PROactive, had previously been scrutinised by the Authority and ruled not to be in breach of the Code. In August 2007 a ruling of no breach was made in relation to the use of cardiovascular claims of benefit from PROactive by Takeda in a mailing (Case AUTH/2011/6/07). In this case '... the Panel did not consider the study was a "negative" study the Panel considered that as the primary end point showed a trend in favour of pioglitazone, and the statistical significance of that endpoint had been explained at the outset, it was not misleading to give details of the secondary endpoints'.

Other than Lincoff *et al* and PROactive, only one other analysis of ischaemic CV outcomes had been published. This meta-analysis of pioglitazone data had been published by Mannucci *et al* (2008). The meta-analysis included studies not limited to type 2 diabetes and did not utilise patient-level data, whilst evaluating different endpoints to those evaluated by Lincoff *et al*; however, results also showed a trend towards benefit for non-fatal coronary events, which although this was not statistically significant, was nonetheless of a similar magnitude to that seen by Lincoff *et al*.

As clearly laid out in the inter-company correspondence to date, the validity of PROactive data was first questioned by Merck Sharp & Dohme in its initial complaint to Takeda. The discussion that ensued regarding PROactive was merely in response to the concerns raised by Merck Sharp & Dohme. The meta-analysis (which contained a significant proportion of patients from PROactive (32% of the entire population and 55% of patient-years)) alone provided substantiation for the claim of ischaemic event reduction.

Takeda noted Merck Sharp & Dohme's comment that claims of such all-embracing significance required appropriate substantiation, and that Lincoff *et al* did not represent such evidence, the authors having acknowledged the meta-analysis had 'important limitations'.

Takeda noted however that most clinical trials and meta-analysis had 'important limitations' and that Lincoff *et al* immediately followed their comment with 'Nevertheless, because all of the trials used for this analysis were double-blinded and randomized, **potential biases introduced by these limitations should be minimized**' (Takeda's emphasis).

Takeda was concerned that Merck Sharp & Dohme had denigrated the quality of Lincoff *et al*, which underwent a rigorous peer-review prior to publication in the Journal of the American Medical Association (JAMA), a well-respected international journal with a high impact factor. Lincoff *et al* stated: 'A database containing individual patient data collected during eligible clinical trials of pioglitazone was transferred by its manufacturer (Takeda, LincolnShire, Illinois) to the Cleveland Clinic Cardiovascular Coordinating Center, an academic research organization in Cleveland, Ohio, for **independent analysis**' (Takeda's emphasis). Furthermore, the disclosure statement on the manuscript detailed the role of the sponsor as: 'The company (Takeda) had been involved in the collection of data for the original trials used for this meta-analysis and participated in the identification of adverse events from records within their database. The company provided that database of eligible trials to the Cleveland Clinic, and did not participate in the statistical analyses used for this publication. The company was not involved in preparing the manuscript and was not permitted to review or comment on the content'. As Takeda had no involvement in either the review or preparation work for the meta-analysis, it regarded the meta-analysis as independent.

Merck Sharp & Dohme's suggestion that the meta-analysis was not independent was not only derogatory to the Cleveland Clinic, but was also inconsistent with current industry practice of funding academic research by means of 'unrestricted educational grants', whereby funders did not have any involvement in the publication or project involvement. Such funded projects were in Takeda's view, appropriately regarded as independent in view of the lack of control or involvement of the funders. By implication, Merck Sharp & Dohme's suggestion undermined both the credibility of academic organizations and healthcare institutions which accepted such unrestricted grants from the pharmaceutical industry as well as the output of such past and future support. To suggest that pharmaceutical companies inappropriately influenced activities which were carried out under unrestricted educational grants risked seriously discrediting and reducing confidence in the pharmaceutical industry as a whole and also ignored the real scientific and patient benefits which flowed from such industry support. Takeda did not endorse Merck Sharp & Dohme's approach and considered that the company should retract its insinuations regarding the Cleveland Clinic.

In view of the arguments set out above Takeda refuted the allegation that the advertisement breached Clause 7.2.

PANEL RULING

The Panel noted Takeda's submissions regarding previous cases and/or previous claims for pioglitazone. In that regard the Panel noted that it considered every case on its own merits. Case precedents were helpful but the complaint made and the material at issue were extremely important and previous rulings of no breach of the Code did not guarantee the same rulings in future with regard to different complaints and different material.

The Panel noted that Actos was licensed for glycaemic control in type 2 diabetes. There was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition.

The Panel noted that the advertisement at issue featured the outline of an overweight man and running the two pages, and across the man's chest was the statement 'ticktock ticktock ticktock ticktock time to act'. This was the dominant image in the advertisement. The spacing between successive ticktocks appeared to decrease as if to suggest a clock speeding up with 'time to act' appearing as an alarm call. The Panel considered that some readers would associate the 'ticktock' phrase, particularly given its positioning over the man's chest, with the heart ie 'ticker'. In that regard the Panel considered that the most prominent visual and text of advertisement suggested cardiovascular issues as opposed to the importance of glycaemic control as submitted by Takeda.

The claim, which ran down the right-hand side of the advertisement, was one continuous statement: 'Pioglitazone sustains glycaemic control but that's not all – in an independent meta-analysis, it has also been shown to reduce ischaemic CV events in Type 2 diabetes'. In that regard the Panel considered that Takeda's description of two claims ('Pioglitazone sustains glycaemic control' followed by a secondary, discursive claim 'shown to reduce ischaemic CV events') with the wording of the second being significantly less prominent than the 'primary claim' was misleading and disingenuous. There was only one claim, all in the same font size and the two components were clearly linked. In the Panel's view the use of the phrase 'but that's not all' suggested that both actions of pioglitazone (glycaemic control and reduction in ischaemic CV events) were of equal importance; some readers would assume that pioglitazone was licensed for both which was not so.

The Panel considered that the claim at issue promoted pioglitazone outwith the terms of its marketing authorization as alleged. The reduction in ischaemic CV events had not been sufficiently clearly placed in the context of being a benefit of glycaemic control. In the Panel's view, given the limited amount of time that people might spend reading a journal advertisement, it was not unreasonable to assume that most readers would read the claim as one simple statement that pioglitazone could be used for glycaemic control and to reduce CV events. A breach of Clause 3.2 was ruled.

The Panel noted that much of the pioglitazone data in Lincoff *et al* was derived from PROactive which had suggested that treatment was beneficial from the cardiovascular standpoint although significant differences were not observed in the pre-specified primary endpoint (death, myocardial infarction, stroke, acute coronary syndrome, leg amputation or coronary or leg revascularization). Lincoff *et al* stated that their results constituted reasonably strong evidence that pioglitazone did reduce the risk of cardiovascular ischaemic endpoints in type 2 diabetes. The Panel noted, however, that the claim at issue stated: '[pioglitazone] has also been shown to reduce ischaemic CV events in Type 2 diabetes'. In that regard the claim went further than Lincoff *et al*. The Panel considered that Lincoff *et al* did not substantiate the robust unqualified claim at issue. The claim was misleading in that regard. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted that the claim referred to Lincoff *et al* as being an independent analysis. At the end of the published paper the authors had acknowledged financial support from Takeda and stated that the company had been involved in the collection of data for the original trials used in the meta-analysis and participated in the identification of adverse events from records within its database. Takeda had provided the database of eligible trials but did not participate in the statistical analyses used for the paper. The company was not involved in preparing the manuscript and was not permitted to review or comment on the content. In the Panel's view Takeda had thus had some involvement in Lincoff *et al* albeit involvement that would not have affected the outcome. Nonetheless the Panel did not consider that describing Lincoff *et al* as independent, in an advertisement, gave the right impression. It implied that Lincoff *et al* was wholly independent of Takeda which was not so – the study had been funded by Takeda and the company had provided or helped to provide some of the data. The Panel thus considered that the phrase 'independent analysis', in the context in which it occurred, was misleading as alleged. A breach of Clause 7.2 was ruled.

With regard to Merck Sharp & Dohme's request that the Panel refer the matter to the ABPI Board of Management with a view to requiring Takeda to issue a retraction, the Panel noted that it could not refer the matter to the ABPI Board. The Appeal Board could require publication of a corrective statement but the Panel could not.

APPEAL BY TAKEDA

Takeda submitted that the advertisement was devised to highlight the importance of glycaemic

control in type 2 diabetes, conveying the need to act for the many patients that were uncontrolled, and to enable health professionals to form their own opinions as to the therapeutic value of using pioglitazone. It was developed to provide the most recent evidence with pioglitazone, at a time when uncertainty existed for health professionals of the glitazone class due to the media coverage on the glitazones and myocardial infarction risk (reported with rosiglitazone) and heart failure risk (seen with both glitazones). Thus the advertisement was designed to clarify the efficacy and safety profile of pioglitazone.

Takeda submitted that it took care to ensure that the overall benefit:risk profile of pioglitazone was represented and that it was clear to the reader that it was first and foremost used for, and licensed in, glycaemic control (as per previous case precedent). The claim regarding reductions in ischaemic CV events was specifically attributed and substantiated by an independent meta-analysis conducted by Lincoff *et al* in which the authors concluded 'the findings of this meta-analysis provide evidence of a favorable effect of pioglitazone on ischemic vascular complications'. More recently Lincoff *et al* had been reviewed by leading independent medical bodies ADA, EASD and NICE), which supported its findings (Nathan *et al* 2008).

The meta-analysis was recognised as independent by the authors ('A database containing individual patient data collected during eligible clinical trials of pioglitazone was transferred by its manufacturer (Takeda, Lincolnshire, Illinois) to the Cleveland Clinic Cardiovascular Coordinating Center, an academic research organization in Cleveland, Ohio, for **independent analysis**.') [emphasis added] who confirmed that whilst Takeda had provided patient level data and funding, it did not participate in the statistical analyses, or in preparing the manuscript and furthermore it was not permitted to review or comment on the contents.

Takeda's understanding of the Panel's ruling was that, consistent with previous case precedent, claims pertaining to additional effects, eg ischaemic CV outcomes data, were acceptable in promotional material. However, its concerns arose surrounding the balance of presentation of the licensed indication and additional effects, the specific wording used in the advertisement to describe the conclusions of Lincoff *et al*, and the use of the word 'independent' to describe the meta-analysis.

Takeda submitted that the points made in its response to the complaint still stood. The key points were as follows

1 Balance of representation of the licensed indication (glycaemic control) and additional ischaemic CV effects – breach of Clause 3.2

Takeda submitted that the interpretation of the visuals and copy was subjective to the reader. During the development of the advertisement, Takeda tested the concept on a number of health professionals to ensure its intention came across correctly in the advertisement. Takeda's intention for the advertisement was as follows.

The visual was typical of a patient with type 2 diabetes, with the 'ticktock ticktock' theme representative of a 'call to action' for the health professional to act, ie it suggested time passing. In the UK, a vast number of patients with type 2 diabetes were uncontrolled and would benefit from a change in, or an additional, medication (for example, the quality outcomes frame work (QOF) target in England for achievement of the HbA1c target of ≤ 7.5 was found to be only 66.8% in 2007/08, thus leaving a large population not achieving this audit target (Lincoff *et al*)). The design of the visual, was so that 'ticktock ticktock' emphasised this impending need to manage the progression of the disease, and drew attention first to the man, typical of a patient with type 2 diabetes, and then to the headline 'time to act' followed by the copy, brand names and heart failure warnings. Therefore, the 'ticktock ticktock' wording was used to firstly position the theme of time and secondly to link from the visual to the copy.

The 'ticktock ticktock' line was not designed with decreasing gaps, as suggested by the Panel. The gaps were designed for readability, as the wording spanned the man's body as well as the centrefold of the journal.

First and foremost, the claim stated that pioglitazone sustained glycaemic control – this was first, before any statement about ischaemic CV effects. The advertisement then went on to state 'but that's not all – in an independent meta-analysis, it has also been shown' – to ensure the reader saw the claim that followed (to reduce ischaemic CV events) was supported by the meta-analysis and not specifically attributed to the SPC, thus being in the context of the licensed indication (glycaemic control).

The basis for the claim on ischaemic CV event reduction was Lincoff *et al*, with the claim specifically attributed to the Lincoff *et al* meta-analysis, rather than appearing as a claim from the SPC. This was to ensure there was a clear separation from the licensed indication and any additional benefits seen on ischaemic CV events.

All the patients in the meta-analysis had uncontrolled type 2 diabetes (ie the observed CV effect was in patients with a licensed indication for pioglitazone's use). Takeda therefore considered the follow-up claim of ischaemic CV event reduction was adequately set in the context of glycaemic control.

It was widely recognised that the main purpose of glycaemic control was to reduce the risk of

complications (NICE). It had been noted that 80% of patients with type 2 diabetes would die prematurely from CVD (Barnett *et al* 2003), therefore it was especially important for prescribers to know of any additional evidence that confirmed this benefit with an oral anti-hyperglycaemic agent.

2 The robustness and validity of using Lincoff *et al* to substantiate the claim 'shown to reduce ischaemic CV events' – breaches of Clauses 7.2 and 7.4

Takeda submitted that the Panel's statement that 'Lincoff *et al* stated that their results constituted reasonably strong evidence that pioglitazone did reduce the risk of ischaemic cardiovascular ischaemic endpoints in type 2 diabetes' differed from the conclusions given by Lincoff *et al*. This stated 'Pioglitazone is associated with a significantly lower risk of death, myocardial infarction or stroke among a diverse population of patients with diabetes' and 'In conclusion, the findings of this meta-analysis provide evidence of a favorable effect of pioglitazone on ischemic vascular complications'. Therefore, the wording in the advertisement, that 'it has also been shown to reduce ischaemic CV events' reflected and did not go further than Lincoff *et al*. Lincoff *et al* did not state that the evidence was 'reasonably strong' as suggested by the Panel.

The meta-analysis was conducted by the Cleveland Clinic in the US. The Cleveland Clinic Lerner Research Institute was the fifth largest research institute in the US and in 2007, research from the Cleveland clinic appeared in 1,196 publications, including 1,060 journal articles, 126 book chapters and 10 books. Many of these were in highly respected peer-reviewed high-impact journals, as was the meta-analysis in question which was published in JAMA.

A similar meta-analysis conducted by the Cleveland Clinic (which was slightly less robust in design as patient level data was not available for analysis) for rosiglitazone had been widely publicised (Nissen *et al* 2007) and having been reviewed by regulatory authorities in the US and Europe had resulted in licence changes for rosiglitazone issued by the FDA and the EMEA. Other meta-analyses conducted by the same group had resulted in medicines being withdrawn from development (eg muraglitazar (Nissen *et al* 2005)) or from the market (Vioxx (Nissen *et al* 2001)). Both meta-analyses evaluating muraglitazar and Vioxx were published in the same journal as Lincoff *et al*, ie JAMA.

Takeda had recently discussed and agreed the use of ischaemic CV claims, based on the Lincoff *et al* with the MHRA which confirmed that it was acceptable to make claims relating to ischaemic CV events from this study, providing they were placed in context of safety, with guidance detailed on the monitoring requirements for heart failure and the contraindication for use in heart failure (all of which was included in the advertisement in question).

A number of independent medical and scientific bodies had recently reviewed the data from Lincoff *et al*:

NICE recently issued updated draft guidance for consultation on newer agents in the management of type 2 diabetes. The guidelines development group (consisting of leading UK experts in diabetes), reviewed the Lincoff *et al* data and stated 'One meta-analysis (Lincoff *et al* 2007) showed a reduced risk of death, myocardial infarction or stroke associated with the use of pioglitazone' and 'the current evidence suggests that rosiglitazone increases the risk of heart attacks and cardiovascular mortality but that pioglitazone reduces it'. The ADA and EASD recently issued an updated consensus statement on the management of type 2 diabetes, having reviewed the ischaemic CV outcomes data (including Lincoff *et al*); they also recognised 'a potential decrease in MI' with pioglitazone (Nathan *et al*).

3 Was Lincoff *et al* independent?

Lincoff *et al* stated: 'A database containing individual patient data collected during eligible clinical trials of pioglitazone was transferred by its manufacturer (Takeda, Lincolnshire, Illinois) to the Cleveland Clinic Cardiovascular Coordinating Center, an academic research organization in Cleveland, Ohio, for **independent analysis**' [emphasis added].

Furthermore, the disclosure statement detailed the role of the sponsor as: 'The company [Takeda] had been involved in the collection of data for the original trials used for this meta-analysis and participated in the identification of adverse events from records within their database. The company provided that database of eligible trials to the Cleveland Clinic, and did not participate in the statistical analyses used for this publication. The company was not involved in preparing the manuscript and was not permitted to review or comment on the contents'.

In view of the absence of any company involvement in either the review or preparation work for the meta-analysis, ie in any of the work fundamental to the meta-analysis, Takeda regarded the meta-analysis as independent.

The suggestion that the meta-analysis was not independent was inconsistent with current industry practice of funding academic research by means of 'unrestricted educational grants', whereby funders did not have any involvement in the publication or project involved. Such funded projects were appropriately regarded as independent in view of the lack of control or involvement of the funders. Indeed, regulatory bodies like the EMEA, received funding and patient level data from pharmaceutical

companies but its independence in evaluation of the data was not in question.

The Panel ruling acknowledged that Takeda had no influence over the outcome or publication of the meta-analysis in its ruling; that Takeda had thus had some involvement in Lincoff *et al*, **albeit involvement that would not have affected the outcome** [emphasis added]. Takeda submitted that this was the most important criterion for whether or not the word independent could be reasonably used.

The suggestion that the meta-analysis was not independent challenged the practice of academic organisations and healthcare institutions in receiving unrestricted grants from the pharmaceutical industry as well as the output of such past and future support. To suggest that pharmaceutical companies inappropriately influenced activities which were carried out under unrestricted educational grants risked reducing confidence in the pharmaceutical industry as a whole.

In conclusion, Takeda emphasised that it was fully committed to compliance with both the letter and the spirit of the Code and had carefully considered the Panel's rulings. It took great care and attention in the preparation of the advertisement in order to ensure that it presented the information in a way that clearly showed the licensed use for pioglitazone before, and above, the additional claim regarding ischaemic CV events. This was further supported by the clear attribution of the additional claim to the independent meta-analysis by Lincoff *et al*. Therefore, Takeda strongly refuted any breaches of the Code.

COMMENTS FROM MERCK SHARP & DOHME

Merck Sharp & Dohme stated that the basis of its case remained as set out in its complaint. However, it would address briefly some of the issues raised by Takeda in its appeal.

1 Balance of advertisement and promotion outside the licence

Merck Sharp & Dohme fully concurred with the Panel's ruling concerning the inappropriate balance of the advertisement, particularly considering the font size, style, graphics, and specific wording of the claim in question. Merck Sharp & Dohme alleged that the clear primary purpose of the advertisement was to communicate the purported effect of pioglitazone on ischaemic heart disease and that this would be the natural inference drawn.

The average reader of the advertisement would be led to believe that Actos and Competact were licensed to reduce the incidence of ischaemic heart disease, in contrast to the position with other treatments for type 2 diabetes. Takeda's appeal, concentrated on the 'balance' arguments referred to above, ignored one of Merck Sharp & Dohme fundamental areas of concern: even if the balance of the claims in the advertisement were more appropriate, and even if they could be more robustly substantiated, Merck Sharp & Dohme alleged that Takeda would not be justified under the Code in making ischaemic heart disease reduction claims for pioglitazone within the terms of its current licence.

While ischaemic heart disease was a well-recognised long-term complication of type 2 diabetes, it was not the same disease entity. Pioglitazone was licensed only for glycaemic reduction in type 2 diabetes, and not for prevention of ischaemic heart disease. The pioglitazone SPC did not refer to any beneficial effects of pioglitazone on ischaemic heart disease status. The relationship between improvements in glycaemic control and reduction in ischaemic heart disease rate remained controversial, certainly within the time-frames of the studies included in Lincoff *et al*. Finally, Lincoff *et al* specifically stated that the effect of pioglitazone on ischaemic heart disease, if real, 'is distinct from the efficacy of thiazolidinediones in reducing blood glucose levels', whereas pioglitazone did not have a licence for any such extra-glycaemic effect.

Should there be sufficient evidence to warrant ischaemic heart disease reduction claims, this evidence should be submitted to the appropriate regulatory authorities with a view to securing a licence amendment. As matters stood, there was a considerable history of claims concerning the 'ancillary' effects of products coming before the Panel and Appeal Board, particularly in the therapy area of diabetes. Merck Sharp & Dohme therefore asked the Appeal Board to make an explicit judgement on this matter, if only to avoid the necessity for such cases in the future.

2 Heart failure

Merck Sharp & Dohme noted that Takeda had stated in its appeal that the advertisement was designed to clarify the efficacy and safety profile of pioglitazone. It also explicitly mentioned the current uncertainty of health professionals regarding the heart failure risk seen with glitazones.

Merck Sharp & Dohme's concerns about the issue of heart failure were expressed in its complaint, but were not considered by the Panel, as they had not been subject to adequate inter-company dialogue. However, since this issue had been raised by Takeda at appeal, Merck Sharp & Dohme alleged that the meta-analysis on which the ischaemic heart disease claim was based also noted a significant increase in heart failure incidence in pioglitazone-treated patients. In fact, this finding had a lower p-value than the ischaemic heart disease data. By focussing solely on the positive aspects of the meta-analysis, the

advertisement did not accurately present the totality of the data with respect to important issues of patient safety, and was therefore biased and misleading, representing a further and separate breach of Clause 7.2. As this focussed on one particular positive aspect of the data it did not encourage rational prescribing, and was directly related to patient safety, Merck Sharp & Dohme considered the issue to be of the utmost seriousness.

3 Substantiation

Merck Sharp & Dohme noted Takeda's comments concerning reactions to Lincoff *et al* and similar meta-analysis. Merck Sharp & Dohme alleged that the situation was, however, far less clear-cut than these comments suggested. In fact, there was intense controversy within the diabetes community with respect to the significance, validity, applicability and implications of both the rosiglitazone and pioglitazone meta-analyses.

That said, the true issue in question was whether, under the Code, Takeda was justified in making all-embracing claims on the basis of a single meta-analysis involving often clearly inappropriate studies, none of which were designed or powered to demonstrate the primary outcome benefit being claimed. Although Merck Sharp & Dohme had no objection in general to the appropriate use of meta-analysis data in supporting product claims, Lincoff *et al* alone did not adequately substantiate the claim in question.

4 Use of the word 'independent'

By questioning the use of the word 'independent' in reference to Lincoff *et al*, it was not, of course, Merck Sharp & Dohme's intention to impugn in any way the integrity of the academic centre that performed the analysis. The fact that Takeda supplied the centre with all the data used in the analysis, in itself, rendered the description of 'independent' inappropriate. Further, there was a widely acknowledged general perception that studies could not be considered as truly independent if they were wholly funded by the organisation whose product was being investigated.

Merck Sharp & Dohme had no reason to doubt that the meta-analysis was conducted by the centre concerned with all due ethical and scientific rigour. This did not alter the fact that there were well-defined expectations attached to the use of such terms as 'independent'. These expectations were patently not met in the present case, and Merck Sharp & Dohme therefore maintained that the use of the term in the advertisement was improper and misleading.

In light of the above, and the detailed representations made in its complaint, Merck Sharp & Dohme asked the Appeal Board to uphold the Panel's rulings.

Merck Sharp & Dohme noted that in its original submission, it asked the Panel to consider referring the case to the ABPI Board of Management with a view to requiring Takeda to issue a formal retraction of the claims made in the advertisement, together with a corrective statement. The Panel informed Merck Sharp & Dohme in its ruling that only the Appeal Board could so act. Given that this matter was now before the Appeal Board and in the event that the Appeal Board upheld the Panel's rulings, Merck Sharp & Dohme reiterated its request that further sanctions be considered, particularly in view of the length of time that health professionals had been exposed to these materials.

APPEAL BOARD RULING

The Appeal Board noted there was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition.

The Appeal Board examined the advertisement at issue which featured the outline of an overweight man and running across the two pages, and across the man's chest, and thus his heart, was the statement 'ticktock ticktock ticktock ticktock time to act'. This was the dominant image in the advertisement. The spacing between successive ticktocks appeared to decrease as if to suggest a clock speeding up with 'time to act' appearing as an alarm call. The Appeal Board considered that some readers would associate the 'ticktock' phrase, particularly given its positioning over the man's chest, with the heart ie 'ticker'. In that regard the Appeal Board considered that the most prominent visual and text of the advertisement suggested cardiovascular issues as opposed to the importance of glycaemic control as submitted by Takeda.

The Appeal Board considered that the claim at issue, which ran down the right-hand side of the advertisement, 'Pioglitazone sustains glycaemic control, but that's not all – in an independent meta-analysis, it had also been shown to reduce ischaemic CV events in Type 2 diabetes'. was one continuous statement, and not two claims ('Pioglitazone sustains glycaemic control' followed by a secondary, discursive claim 'shown to reduce ischaemic CV events') as submitted by Takeda. The entire claim was the same font size and the two components were clearly linked. The Appeal Board considered that some readers would therefore assume that pioglitazone was licensed for both glycaemic control and reduction of ischaemic CV events which was not so.

The Appeal Board considered that the claim at issue together with the visual promoted pioglitazone outwith the terms of its marketing authorization as alleged. The reduction in ischaemic CV events had not been sufficiently clearly placed in the context of being a benefit of

glycaemic control. It was not unreasonable to assume that most readers would read the claim as one simple statement: that pioglitazone could be used for glycaemic control and to reduce CV events. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful.

The Appeal Board considered that the undue emphasis placed on the reduction of ischaemic CV events by pioglitazone was misleading and it upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

The Appeal Board considered that the particular claim regarding the reduction of CV events was capable of substantiation by Lincoff *et al*. Thus the Appeal Board ruled no breach of Clause 7.4. The appeal on this point was successful.

The Appeal Board noted that the particular claim referred to Lincoff *et al* as an independent meta-analysis. At the end of the published paper the authors had acknowledged financial support from Takeda. Takeda had provided the database of eligible trials but did not participate in the statistical analyses used for the paper. The company was not involved in preparing the manuscript and was not permitted to review or comment on the content. In the Appeal Board's view Takeda had no involvement in Lincoff *et al* that would have affected its scientific rigour and outcome. Nonetheless describing Lincoff *et al* as independent, in the advertisement, gave a misleading impression. Those reading the advertisement would not have the benefit of the declaration of financial support given in Lincoff *et al*. The claim implied that Lincoff *et al* was wholly independent of Takeda which was not so – funding and data had been provided by Takeda and this would not be clear from the use of the word 'independent' in the advertisement. The Appeal Board thus considered that the phrase 'independent meta-analysis', in the advertisement, was misleading as alleged. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2.

The Appeal Board did not consider the circumstances warranted additional sanctions as requested by Merck Sharp & Dohme.

Complaint received **1 September 2008**

Case completed **16 February 2009**

CASE AUTH/2177/10/08

ALLERGAN v MERZ PHARMA

Xeomin leavepiece

Allergan complained about a leavepiece for Xeomin (Botulinum neurotoxin type A) issued by Merz Pharma. Allergan supplied Botox (Botulinum neurotoxin type A). Merz's product, unlike Allergan's, was free from complexing proteins.

As the complaint implied that Merz had breached its undertaking given in Case AUTH/2119/4/08 that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

The detailed response from Merz is given below.

The claim 'The first Botulinum neurotoxin free from complexing proteins' was the title of the leavepiece and appeared in association with the image of a horse chestnut emerging from its spiky shell.

Allergan noted that the claim was placed above the image of a horse chestnut (the neurotoxin) emerging from a spiky shell (the complexing proteins). Allergan alleged this statement, when associated with the image, implied some special merit for Xeomin associated with the removal of the complexing proteins, versus other neurotoxins on the market.

Allergan believed that the special merit which was implied must relate to a benefit gained from the removal of the complexing proteins. The back page of the leavepiece inferred some potential benefit from the lack of complexing proteins with the claim 'Low foreign protein load suggests low potential for neutralising antibody formation'. However this suggestion had not been demonstrated clinically. In fact, in a journal advertisement (the subject of Case AUTH/2119/4/08) the above claim was qualified with the statement 'These observations have not been confirmed in the clinical setting'.

In addition, as concluded in Case AUTH/2119/4/08, the role of complexing proteins was still the subject of scientific debate. It was thought that the accessory proteins might confer an advantage in persistency in the target muscle versus naked neurotoxin. This issue had not been resolved in favour of one generally accepted viewpoint. Allergan alleged that the claim with the associated visual implied an advantage for Xeomin versus other Botulinum toxin products with complexing proteins and some special merit for Xeomin above other Botulinum toxins on the market.

Therefore, Allergan alleged that the claim 'The first Botulinum neurotoxin free from complexing proteins' when associated with the image of the horse chestnut and spiky shell was misleading and implied a special merit for Xeomin which could not be substantiated.

The Panel noted that in Case AUTH/2119/4/08, it had considered the claim 'Neurotoxin you need – complexing proteins you don't' in association with the picture of a horse chestnut emerging from its spiky shell. The Panel, *inter alia*, considered that the claim implied a proven clinical disadvantage for those Botulinum toxin type A products associated with complexing proteins for which there was no supporting data. This impression was strengthened by the picture of the chestnut (the neurotoxin) and its spiky shell (the complexing proteins). The Panel considered that the claim was misleading and a breach of the Code had been ruled.

The Panel noted that the claim now at issue, 'The first Botulinum neurotoxin free from complexing proteins' was different to that at issue in Case AUTH/2119/4/08 although, as before, it appeared above the image of the horse chestnut emerging from its spiky shell. The claim itself was a statement of fact and was substantiated by the cited reference (Benecke *et al* 2005) and by the summary of product characteristics (SPC). Nonetheless the Panel considered that even when a claim was true, the context in which it was used was very important. The front page of the leavepiece at issue consisted almost solely of the claim, the horse chestnut visual and the product logo which also incorporated the strapline '*Free* from complexing proteins'. Given the spiky shell of the horse chestnut, the Panel considered that the front page of the leavepiece implied that there was something injurious about complexing proteins, that they were deemed an unnecessary 'hazard' and that there was some special merit or clinical advantage if a Botulinum neurotoxin was free of such proteins. The claim would be assumed to be of clinical consequence. The Panel considered that the claim was misleading as alleged. Breaches of the Code were ruled.

Upon appeal by Merz, the Appeal Board considered that regardless of the fact that the claim was true, in the context of the image of the horse chestnut it implied a special merit or clinical advantage for Xeomin. There was no evidence that removing the complexing proteins from the Botulinum neurotoxin conferred any clinical advantage. The Appeal Board upheld the Panel's rulings of breaches of the Code.

Allergan alleged that the image itself was misleading since it was clearly intended to represent the neurotoxin as a smooth and attractive nut and the complexing protein as a

prickly and potentially injurious outer casing.

As stated above, and as concluded in Case AUTH/2119/4/08, the role of complexing proteins was still the subject of scientific debate; it was thought that they might confer an advantage in persistency in the target muscle versus naked neurotoxin.

The Panel noted its comments above. The Panel further noted that the specific role of complexing proteins was the subject of scientific debate as acknowledged by Merz. The Panel considered that associating Xeomin with the horse chestnut visual implied that Xeomin was free of some superfluous, unwanted and possibly injurious element that was otherwise associated with other Botulinum neurotoxins. The Panel considered that the horse chestnut image, and the messages it implied, was misleading. A breach of the Code was ruled.

Upon appeal by Merz, the Appeal Board considered that the image and the messages it portrayed were misleading and upheld the Panel's ruling of a breach of the Code.

Allergan alleged that the claim 'Low foreign protein load suggests low potential for neutralising antibody formation' was misleading as this observation had not been confirmed in a clinical setting. In a recent Xeomin journal advertisement this claim was qualified with the statement 'These observations have not been confirmed in the clinical setting'. A study in rabbits had shown that Xeomin was not associated with any biologically relevant immunogenicity. However, the clinical relevance of this data had yet to be confirmed and long-term use of Xeomin had yet to be investigated (Jost *et al* and Bluemel *et al*).

The two references cited by Merz to support the claim (Jost *et al* and Benecke *et al*) stated that clinical studies were required to confirm this observation in an animal model and that 'this issue should be assessed in long-term safety studies with antibody testing' (Benecke *et al*).

The Panel noted that it was an established principle under the Code that all claims related to the clinical situation unless otherwise stated. The supplementary information stated that care must be taken with the use of data derived from *in vitro* studies, studies in healthy volunteers and in animals so as to not mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance.

The Panel noted that the claim at issue was referenced to Jost *et al* which was a review of the pre-clinical and clinical development of Xeomin. A pre-clinical antigenicity study in rabbits suggested that it would be unlikely that therapy would fail due to antibody formation over long-term use (Bluemel *et al*). Jankovic *et al* had compared the antibody levels produced following the clinical use of two Botulinum neurotoxin type A preparations, one with 25ng protein/100u and the other with 5ng protein/100u. It appeared that extrapolation of those results had led Jost *et al* to state that [Xeomin] was likely to be associated with fewer neutralising antibodies and reduced numbers of secondary non-responders. At the end of their 'discussion' section, Jost *et al* stated that future studies should focus on the administration of Xeomin in Botulinum-A-naive patients, with the aim of investigating its antigenic properties, and determining long-term efficacy and safety profiles.

The Panel noted that although the claim 'Low foreign protein load *suggests* low potential for neutralising antibody formation' (emphasis added) did not directly refer to Xeomin, it was an integral part of the Xeomin leavepiece and was a claim for the product. The Panel did not accept the implication that it would be read as a general scientific proposition. The Panel noted that clinically, the antigenic potential of Xeomin had still to be established. The Panel thus considered that in that regard the claim was misleading as alleged. The use of the word 'suggests' did not negate the impression that a low potential for neutralising antibody formation with Xeomin had been proven. A breach of the Code was ruled.

Upon appeal by Merz, the Appeal Board noted that although the claim did not directly refer to Xeomin, it was an integral part of the Xeomin leavepiece and was a claim for the product. The Appeal Board noted that clinically the antigenic potential of Xeomin had still to be established. The Appeal Board considered that the claim was misleading and it upheld the Panel's ruling of a breach of the Code.

The alleged breach of undertaking was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

The Panel noted that in the previous case, Case AUTH/2119/4/08, Allergan had complained about the claim 'Neurotoxin you need – complexing protein you don't'. The Panel had considered the claim in association with the image of the horse chestnut emerging from its spiky shell. The Panel, *inter alia*, considered that the claim implied a proven clinical disadvantage for those Botulinum neurotoxin type A products associated with complexing proteins for which there was no supporting data. The impression was strengthened by the picture of the chestnut (the neurotoxin) and its spiky shell (the complexing proteins). The Panel considered that the claim was misleading and a breach of the Code was ruled.

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that

companies complied with undertakings.

The Panel noted its comments and ruling above and considered that the messages conveyed in the leavepiece now at issue were closely similar to those considered in Case AUTH/2119/4/08 and were covered by the undertaking given in that case. Given that the leavepiece implied a clinical disadvantage for Botulinum neurotoxins with complexing proteins, the Panel considered that Merz had not complied with its undertaking. A breach of the Code was ruled. High standards had not been maintained and a further breach was ruled. The Panel considered that in breaching its undertaking Merz had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Upon appeal by Merz the Appeal Board considered that the claim at issue 'The first Botulinum neurotoxin free from complexing proteins' was different to the claim at issue in Case AUTH/2119/4/08 'Neurotoxin you need – complexing protein you don't'. The Appeal Board noted that the image of the horse chestnut accompanying both claims was the same. There had been no ruling specifically related to the image in Case AUTH/2119/4/08. The Appeal Board noted that Merz had taken steps to comply with its undertaking given in Case AUTH/2119/4/08. The Appeal Board did not consider that the current material meant that Merz had breached its undertaking and no breach of the Code was ruled.

Allergan Ltd complained about a leavepiece (ref 1056/XEO/MAY/2008/SM) for Xeomin (Botulinum neurotoxin type A) issued by Merz Pharma UK Ltd. Allergan supplied Botox (Botulinum neurotoxin type A). Merz's product, unlike Allergan's, was free from complexing proteins.

Inter-company correspondence had failed to satisfy Allergan's concerns.

As the complaint implied that Merz had breached its undertaking given in Case AUTH/2119/4/08 that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. Merz was accordingly asked to comment in relation to Clauses 2, 9.1 and 25 of the Code in addition to the clauses cited by Allergan.

1 Claim 'The first Botulinum neurotoxin free from complexing proteins'

This was the title of the leavepiece and appeared in association with the image of a horse chestnut emerging from its spiky shell.

COMPLAINT

Allergan noted that the claim was placed above the image of a horse chestnut (the neurotoxin) emerging from a spiky shell (the complexing proteins). Allergan alleged this statement, when associated with the image, implied some special merit for Xeomin associated with the removal of the complexing proteins, versus other neurotoxins on the market.

Allergan believed that the special merit which was implied must relate to a benefit gained from the removal of the complexing proteins. The back page of the leavepiece inferred some potential benefit from the lack of complexing proteins with the claim 'Low foreign protein load suggests low potential for neutralising antibody formation'. However this suggestion had not been demonstrated clinically. In fact, in the Xeomin advertisement in the BMJ, 15 March 2008, (ref 1012a/XEO/NOV/2007 – the subject of Case AUTH/2119/4/08) the above claim was qualified with the statement 'These observations have not been confirmed in the clinical setting'. A study in rabbits had shown that Xeomin was not associated with any biologically relevant immunogenicity. However, as Merz's advertisement stated, the clinical relevance of these data had yet to be confirmed and long-term use of Xeomin had yet to be investigated (Jost *et al* 2007 and Bluemel *et al* 2006).

In addition, as concluded in Case AUTH/2119/4/08, the role of complexing proteins was still the subject of scientific debate. It was thought that the accessory proteins might confer an advantage in persistency in the target muscle versus naked neurotoxin. Certainly, this issue of the role of complexing proteins had not been resolved in favour of one generally accepted viewpoint. Allergan alleged that the claim with the associated visual implied an advantage for Xeomin versus other Botulinum toxin products with complexing proteins and some special merit for Xeomin above other Botulinum toxins on the market.

In its response Merz stated that this implication was 'incomprehensible' but did not further address Allergan's concerns. Whilst the special merit or advantage being claimed might not be clear to the reader and might be left to their imagination, Allergan strongly believed that the claim and visual implied an unsubstantiated advantage.

Therefore, Allergan alleged that the claim 'The first Botulinum neurotoxin free from complexing proteins' when associated with the image of the horse chestnut and spiky shell was in breach of Clauses 7.2 and 7.10 as it was misleading and implied a special merit for Xeomin which could not be substantiated.

RESPONSE

Merz noted that the Xeomin summary of product characteristics (SPC) clearly stated that Xeomin was free from complexing proteins. No other commercially available Botulinum neurotoxin was free from complexing proteins. Based on this, the claim was true, accurate and unambiguous.

The claim was supported with an image of a horse chestnut emerging from its shell. Merz believed that the image was an appropriate metaphor to support the claim '... free from complexing proteins'. The metaphor was chosen as it captured the role of the complexing proteins in an accessible and meaningful way.

In nature the highly active neurotoxin was protected by an outer casing of complexing proteins including haemagglutinins and non-toxic, non-haemagglutinin proteins. It was generally accepted that the primary role of the complexing proteins was to protect the neurotoxin from the harsh acid conditions of the stomach when the toxin was ingested. Studies of the 900kD neurotoxin complex had demonstrated that once the complex passed from an acidic pH environment to one of a physiological pH there was a rapid disassociation of the neurotoxin and the protective protein complex with the complex breaking into a number of fragments. This disassociation occurred in minutes compared with the onset of therapeutic effect which was measured in days (Eisele and Taylor 2008).

The horse chestnut represented a clear metaphor of this process with the outer casing of the shell providing robust protection of the fragile nut as it was delivered from the tree to its site of action, the soil. Once in place the nut was released from its protective shell and was able to perform its functional role, becoming a new tree.

Merz believed that this was a clear and unambiguous metaphor which reinforced the accurate claim that Xeomin was the first neurotoxin free from complexing proteins and as such denied that the image and copy were a breach of Clause 7.2.

Allergan asserted that the metaphor implied special merit for Xeomin which it supported with reference to the claim found later in the leavepiece, that a 'Low foreign protein load suggests low potential for the neutralising antibody formation'. As this paragraph was not associated with an allegation of a breach of the Code it would be dealt with later.

Merz challenged the assertion that the claim 'The first Botulinum neurotoxin free from complexing proteins' and the use of an unambiguous image/metaphor to support it exaggerated the properties or implied some special merit of Xeomin. Xeomin was free from complexing proteins, a fact stated in its SPC, and as such Merz refuted the assertion that the claim and supporting image were in breach of Clause 7.10.

PANEL RULING

The Panel noted that in Case AUTH/2119/4/08, it had considered the claim 'Neurotoxin you need – complexing proteins you don't' in association with the picture of a horse chestnut emerging from its spiky shell. The Panel, *inter alia*, considered that the claim implied a proven clinical disadvantage for those Botulinum toxin type A products associated with complexing proteins for which there was no supporting data. This impression was strengthened by the picture of the chestnut (the neurotoxin) and its spiky shell (the complexing proteins). The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

The Panel noted that the claim now at issue, 'The first Botulinum neurotoxin free from complexing proteins' was different to that at issue in Case AUTH/2119/4/08 although, as before, it appeared above the image of the horse chestnut emerging from its spiky shell. The claim itself was a statement of fact and was substantiated by the cited reference (Benecke *et al* 2005) and by the SPC. Nonetheless the Panel considered that even when a claim was true, the context in which it was used was very important. The front page of the leavepiece at issue consisted almost solely of the claim, the horse chestnut visual and the product logo which also incorporated the strapline '*Free* from complexing proteins'. Given the spiky shell of the horse chestnut, the Panel considered that the front page of the leavepiece implied that there was something injurious about complexing proteins, that they were deemed an unnecessary 'hazard' and that there was some special merit or clinical advantage if a Botulinum neurotoxin was free of such proteins. The claim would be assumed to be of clinical consequence. The Panel considered that the claim was misleading as alleged. Breaches of Clauses 7.2 and 7.10 were ruled.

APPEAL BY MERZ

Merz noted that this leavepiece was developed for use with specialist neurologists who were experienced users of Botulinum toxin and familiar with the medicine class and therapeutic area.

Merz noted that the Panel had acknowledged that this claim was a truthful, substantiated statement of fact and that the property was stated explicitly in the SPC and therefore in itself was not misleading.

Merz noted that the Panel had considered that the association of the visual with the claim led to an impression of merit of clinical consequence being formed which was not substantiated and was therefore misleading. Merz submitted that it was not justifiable to rule a statement of fact, which was not misleading, in breach of the Code based upon a visual which was subject to a separate charge. This would preclude the use of a clear statement of fact, as it appeared in the SPC, as a future claim. Merz therefore challenged the validity of the judgement.

However, in defence of the impression created by the claim in association with the visual, Merz submitted that there was merit in removing complexing proteins from Botulinum toxin, that this merit could be substantiated and was of clinical consequence.

Merz submitted that Botulinum toxins occurred in nature and were produced by *Clostridium botulinum* bacteria. The bacteria encased the toxins within complexing proteins to provide protection from protein denaturation by stomach acid prior to absorption through the gastrointestinal tract. On reaching physiological pH the protein complex rapidly dissociated, in less than a minute, into a number of fragments releasing the toxin from its protective coat (Eisele and Taylor). The presence of such proteins allowed the neurotoxin to reach its target and have its effect. This effect was therefore a protective one much like the shell around a horse chestnut.

Merz submitted that in the clinical setting the neurotoxin was not required to pass through the gastrointestinal tract and was injected directly into the target site. Given this, complexing proteins might, in principle, be considered unnecessary for therapeutic efficacy.

Studies into the pharmacodynamics of Xeomin demonstrated that removal of the complexing proteins did not hamper therapeutic efficacy (Xeomin Assessment Report). This had been confirmed in the pivotal phase II and phase III clinical trials for Xeomin which clearly showed that Xeomin had the same clinical efficacy as Botox on a 1:1 dosing ratio, without the need for complexing proteins (Wohlfarth *et al* 2007, Benecke *et al*, Roggenkamper *et al* 2006). This robust clinical evidence remained uncontested.

The safety of Xeomin had been investigated and compared to Botulinum toxins containing complexing proteins in all phases of clinical development. Xeomin had been demonstrated to have equivalent diffusion properties (Wohlfarth *et al*) and safety (Benecke *et al*, Roggenkamper *et al*) to conventional Botulinum toxins. This was recognized by BfArM, the regulatory assessor of the Reference Member State, and was reflected in the conclusion of its medicine safety assessment with the statement:

> 'In summary the overall safety profile of Xeomin is in accordance with the known safety profile of other BoNT/A containing preparations. There were no new safety concerns regarding the safety and tolerability of Xeomin based on the presented clinical studies'.

Merz submitted that the proposition championed by Allergan that there was a current scientific debate on the clinical necessity of complexing proteins was founded on a discussion paper on the cellular origin of neurotoxin and two reviews co-authored by Allergan employees, one of which was published in an Allergan sponsored supplement and contained significant inaccuracies relating to Xeomin (Aoki *et al* 2006).

Johnson and Bradshaw (2001) provided no data on the benefits of complexing proteins (only supposition) but did discuss data on immunogenicity (see below).

Merz submitted that the Allergan paper by Foster *et al* (2006) suggested that the difference in diffusion of toxin complexes in rats was due to differences in the complexing proteins. A similar position was suggested by Aoki *et al*. This data was in rats and the only data in humans contradicted this (Wohlfarth *et al*) leading to the conclusion that the animal data was not of direct relevance to the clinical situation, as required by the Code.

Merz submitted that thus, based upon the efficacy, safety and tolerability profile of Xeomin, a neurotoxin free from complexing proteins, it had been demonstrated that complexing proteins were not required, and therefore could be considered unnecessary, for comparable therapeutic efficacy, safety and tolerability to be achieved.

The confidential assessment report for Xeomin issued by the German regulatory authority, BfArM, clearly identified the merit of removing complexing proteins:

> 'Xeomin (NT 201) is a freeze-dried formulation of botulinum neurotoxin type A (BoNT/A) free of complexing proteins obtained from a well characterised strain of *Clostridium botulinum*. This highly purified nature is therefore thought to represent a clinical advance compared to existing preparations of BoNT/A which contain haemagglutinins.'
>
> 'BoNT/A is obtained from specific strains of *Clostridium botulinum*, and is produced as part of a high molecular weight complex, which is formed by several haemagglutinins and other non toxic proteins. The currently marketed preparations are not free of complexing proteins. They contain other proteins of clostridial origin, which are potentially immunogenic and may lead to the development of antibodies and secondary non-response to treatment.
>
> Immunogenicity is highly relevant to the treatment of focal dystonias as these conditions are chronic and require regular, usually life-long therapy. The proportion of secondary nonresponders to BoNT/A is reported to be around 10%, with a further 40% of treated patients developing titers of non-neutralising antibodies against the haemagglutinins.
>
> Xeomin (NT 201) contains BoNT/A free of complexing proteins, which undergoes a biological manufacturing process to remove accompanying haemagglutinins. In animal models, Xeomin has shown no detectable immunogenicity. This is anticipated to translate into less neutralising antibodies in patients and fewer secondary non-responders upon longterm therapy.'

The assessor went on to further strengthen the merit of removing the natural bacterial defence provided

by the complexing proteins resulting in 'obviously lower toxicity when given by the oral route'.

Merz submitted that the potential for immunogenicity was further expounded in Johnson and Bradshaw provided by Allergan which stated that one of the major drawbacks of the clinical use of Botulinum toxins was the formation of antibodies but provided no data on the positive role of complexing proteins.

Thus complexing proteins could be characterised as potentially immunogenic with the potential to promote antibody formation and secondary non-response. The development of antibodies to a formulation of neurotoxin containing complexing proteins (Botox) and not Xeomin was demonstrated in an animal study (Bluemel *et al*). In the study no neutralising antibodies were produced by Xeomin treated rabbits (0/20) in contrast 20% (4/20) of Botox treated rabbits developed neutralising antibodies.

Merz submitted that in order to confirm the direct relevance of this data to humans the opinion of a World expert in the field was sought. On reviewing the rabbit data Professor Dr H Schellekens, Professor of Immunology, University of Utrech concluded:

> 'Because the microbial product is a foreign protein both for rabbits as well as patients, the reduced immunogenicity seen in rabbits may be extrapolated to patients as has been shown with other microbial products such as asparaginase, adenosinedeamidase (ADA) and staphylokinase. All these products showed both reduction of immunogenicity in animals as well as patients.'

He concluded:

> 'Moreover the magnitude of reduction of immunogenicity seen in rabbits will surely be reflected in reduced immunogenicity in patients.'

Merz submitted that this position, and the authority of Professor Schellekens on the subject, was endorsed by Professor Giovannoni, Neuroscience Centre Lead & Professor of Neurology at Barts and The London School of Medicine and Dentistry, who was a respected UK expert in the field.

Merz submitted that the data clearly showed that complexing proteins increased the potential for neutralizing antibody formation and provided no incremental clinical efficacy, tolerability or safety benefits. Based on this finding it could be concluded that the inclusion of complexing proteins in formulations of Botulinum neurotoxin represented an unnecessary hazard, to which, until now, there had been no alternative.

The low potential for developing neutralising antibodies described above was a direct reflection of the lack of complexing proteins and therefore might be considered a special merit of clinical significance.

Xeomin was a freeze-dried, purified form of Botulinum neurotoxin. Its constituent parts were the pure 150kDa neurotoxin, human albumin and sucrose. Through a process of purification, and the removal of complexing proteins, Merz had developed an inherently stable neurotoxin which had been demonstrated stable at ambient temperature and had a licensed indication for storage at temperatures ≤25°C for up to 3 years from manufacture. By comparison conventional unpurified forms of neurotoxin complexes (Botox and Dysport) required refrigeration (SPC). The special merit resulting from this characteristic, namely reducing the possibility of treatment failure due to failure in the cold chain, was acknowledged in Case AUTH/2119/4/08 and could be considered a merit of clinical significance.

In summary Merz submitted that the claim 'The first Botulinum neurotoxin free from complexing proteins' was a truthful substantiated statement of fact. The associated visual was an appropriate metaphor. The impression created by the visual was not misleading in that complexing proteins had been demonstrated unnecessary and might be considered potentially hazardous. Special merit and clinical advantage for a Botulinum neurotoxin free of such proteins could be substantiated and this view was consistent with the view of the licensing authority.

Further, it was not justifiable to rule a statement of fact, which was not misleading, in breach of the Code based upon a visual which was subject to a separate charge. To pursue a charge which would control the use of an unambiguous and factually accurate statement directly quoted from the SPC represented a position which was not supportable by the letter or the spirit of the Code.

Merz submitted that the evidence demonstrated that there was merit in being free from complexing proteins and therefore the impression created by the claim and associated visual was not misleading and could not be in breach of Clause 7.2. As this impression was accurate it did not exaggerate the properties of Xeomin and could not be in breach of Clause 7.10. In light of this evidence the Panel's ruling of a breach of Clauses 7.2 and 7.10 must be overruled.

COMMENTS FROM ALLERGAN

Allergan noted that Merz now appeared to agree that the claim 'The first Botulinum neurotoxin free from complexing proteins'; when placed above the image of a horse chestnut (the neurotoxin) emerging from a spiky shell (the complexing proteins), implied a special merit for Xeomin vs other toxins on the market. In Merz's response to the complaint it defended the use of the claim as a statement of fact and the horse chestnut image as a clear and unambiguous metaphor to reinforce an accurate claim. Merz had challenged Allergan's assertion that the claim and the image/metaphor

exaggerated the properties or implied some special merit of Xeomin. However, as well as defending the claim as a statement of fact, Merz now appeared to agree that there was both an implied, and indeed an actual special merit in removal of complexing proteins.

Allergan alleged that Merz confirmed that the claim and associated visual were in breach of Clauses 7.2 and 7.10.

Allergan strongly disagreed with the suggestion that there was a special merit of clinical consequence gained for the removal of complexing proteins or that complexing proteins represented an 'unnecessary hazard'.

Allergan agreed that the claim 'The first Botulinum neurotoxin free from complexing proteins' was a statement of fact supported by the Xeomin SPC. However, when associated with the horse chestnut visual this claim was misleading and implied a special merit for Xeomin (the nut) versus Botulinum toxins with complexing proteins (the spiky shell).

Merz clearly believed this to be the case as it defended this impression created by the claim in association with the visual.

Allergan alleged that the clinical evidence presented by Merz did not support its suggestion that complexing proteins represented an 'unnecessary hazard'. The two 16 week non-inferiority studies (Benecke *et al*; Roggenkamper *et al*) cited by Merz had established non-inferiority vs Botox, not clinical equivalence. These studies concluded that both products had comparable safety profiles, with similar adverse event patterns in terms of type and frequency. However, neither supported the supposition that complexing proteins were unnecessary or indeed hazardous. Both studies discussed the potential benefit from a lack of complexing proteins but went on to confirm that this possible benefit had not been demonstrated in a clinical setting. Specifically, Benecke *et al* stated:

> 'Based on its physiochemical properties and toxicologic evidence NT201 [Xeomin] is expected to lead to a reduced incidence of non-responders after long term treatment as described for other marketed BTX-A products. This issue should be assessed in long-term safety studies with antibody testing.'

Similarly, Roggenkamper stated:

> 'There is good nonclinical evidence that NT201 will be less immunogenic than BOTOX, owing to the high purified preparation and absence of immunologenic proteins. Thus NT201 may specifically be of therapeutic value in the long-term treatment of blepharospasm. Firm proof, however, warrants long-term clinical studies in conjunction with antibody tests'.

Allergan noted the phase 2 study in 32 volunteers (Wohlfarth *et al*) demonstrated that both Botox and Xeomin were effective and well tolerated in healthy male subjects. In this model the desired paretic effect was observed for both products with no diffusion into adjacent muscles. However, this study did not support the supposition that complexing proteins were 'unnecessary' or 'hazardous'. There were a significant number of non-clinical publications discussing the role of complexing proteins. Indeed, as concluded in Case AUTH/2119/4/08, the role of complexing proteins was still the subject of scientific debate (Aoki *et al*; Foster *et al*; Johnson and Bradshaw). Certainly, the issue of the role of complexing proteins had not been resolved in favour of one generally accepted viewpoint.

Allergan noted that Merz had presented a section from the assessment report for Xeomin issued by the BfArM to support its argument that complexing proteins were an unnecessary hazard. The section stated that in animal models Xeomin had shown no detectable immunogenicity and that this was anticipated to translate into less neutralizing antibodies (emphasis added). To date, the only available data on immunogenicity was in rabbits which had shown that Xeomin was not associated with any biologically relevant immunogenicity in this model (Bluemel, *et al*). Although, to be accurate, one rabbit developed ELISA detectable antibodies after Xeomin treatment (Jost, *et al*). The clinical relevance of the rabbit data had yet to be confirmed and long-term use of Xeomin had yet to be investigated (Jost, *et al*).

In contrast, there was a wealth of long-term clinical data regarding antibody formation following injections of Botox. Overall, neutralizing antibody formation was rare with the current preparation of Botox (Brin *et al* 2008; Mejia *et al* 2005; Yablon *et al* 2007).

The expert statement and implication of potential benefit to patients from reduced immunogenicity in rabbits, did not, in Allergan's view, warrant the conclusion of Merz that the inclusion of complexing proteins in formulations of Botulinum neurotoxin represented an unnecessary hazard.

Allergan did not agree that a lack of complexing proteins was a special merit of clinical significance. The ability to store Xeomin at room temperature (prior to reconstitution) did not provide a special merit of clinical significance. In Case AUTH/2119/4/08 the above property was considered to have important practical implications for the customer. It was disingenuous to now suggest that the claim at issue, in association with the visual was used to support the special merit that no refrigeration was required prior to reconstitution. The special merit of clinical significance being implied was a low foreign protein load suggesting a low potential for neutralizing antibody formation which had not yet

been demonstrated in clinical practice.

In addition, Allergan was not aware of any data to support the suggestion that the removal of complexing proteins accounted for the ability to store Xeomin at room temperature. Indeed, it was likely that the addition of more human serum albumin (a known stabilising agent) to Xeomin (1g in Xeomin vs 0.5g in Botox) provided sufficient stabilization to enable storage at room temperature. Thus, the ability to store Xeomin at room temperature (prior to reconstitution) was likely to be a function of formulation.

In summary, Allergan submitted that the claim 'The first Botulinum neurotoxin free from complexing proteins' when associated with the image of the horse chestnut and spiky shell was in breach of Clauses 7.2 and Clause 7.10; it was misleading and implied a special merit for Xeomin which could not be substantiated.

Allergan did not agree with the view presented by Merz that a statement of fact could not be ruled as misleading. In this case, with the context of the associated visual, the statement was indeed misleading.

APPEAL BOARD RULING

The Appeal Board noted that the claim 'The first Botulinum neurotoxin free from complexing proteins' was a statement of fact taken from the Xeomin SPC. It would encourage readers to consider the clinical benefits that arose from Xeomin being free from complexing proteins. The Appeal Board considered that the image of the horse chestnut implied that the nut (Xeomin), which represented the purified neurotoxin protein, was the necessary element and that the spiky shell (complexing proteins), which were absent in Xeomin but present in other Botulinum neurotoxins, were an unnecessary hazard.

The Appeal Board considered that regardless of the fact that the claim was true, in the context of the image of the horse chestnut it implied a special merit or clinical advantage for Xeomin. There was no evidence that removing the complexing proteins from the Botulinum neurotoxin conferred any clinical advantage. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.10. The appeal on this point was unsuccessful.

2 The horse chestnut visual

COMPLAINT

Allergan believed that the image itself was misleading since it was clearly intended to represent the neurotoxin as a smooth and attractive nut and the complexing protein as a prickly and potentially injurious outer casing.

As stated above, and as concluded in Case AUTH/2119/4/08, the role of complexing proteins was still the subject of scientific debate; it was thought that they might confer an advantage in persistency in the target muscle versus naked neurotoxin (Aoki *et al*; Foster *et al* and Johnson and Bradshaw).

Allergan did not agree with Merz's view that the horse chestnut seed and shell was an accurate metaphor in relation to Botulinums. In fact its argument that 'the horse chestnut seed does not need the spiky shell to provide its end effect' was at odds with the conclusions of Case AUTH/2119/4/08. The 'shell' (or complexing proteins) might influence where the 'nut' (or neurotoxin) acted in the target muscle and hence might influence its clinical effect.

Allergan alleged that the image was in breach of Clause 7.8.

RESPONSE

Merz stated that, as discussed in point 1 above the horse chestnut metaphor was chosen as it captured the role of the complexing proteins in an accessible and meaningful way.

As previously stated, in nature the highly active neurotoxin was protected by an outer casing of complexing proteins including haemagglutinins and non-toxic, non-haemagglutinin proteins. It was generally accepted that the primary role of the complexing proteins was to protect the neurotoxin from the harsh acid conditions of the stomach when the toxin was ingested. Studies of the 900kD neurotoxin complex had demonstrated that once the complex passed from an acidic pH environment to one of a physiological pH there was a rapid disassociation of the neurotoxin and the protective protein complex with the complex breaking into a number of fragments. This disassociation could be measured in minutes compared with the onset of therapeutic effect which was measured in days (Eisele and Taylor).

The horse chestnut represented a clear metaphor of this process with the outer casing of the shell providing robust protection of the fragile nut as it was delivered from the tree to its site of action, the soil. Once in place the nut was released from its protective shell and was able to perform its functional role, becoming a new tree.

Allergan asserted that the image was misleading in representing the neurotoxin as smooth and attractive and the complexing proteins as prickly and injurious. The complexing proteins which surrounded it, made up of haemagglutinins and non-toxic, non-haemagglutinin proteins, provided stability and protection for the neurotoxin. Presenting Botulinum as a fragile nut surrounded by the robust protection of its shell was consistent with the function and form of Botulinum

neurotoxin *in vivo* and as such was neither misleading nor inappropriate. Merz denied a breach of Clause 7.8.

Allergan also asserted that this metaphor did not allow for potential benefits afforded by the presence of complexing proteins. Merz accepted that the specific role of complexing proteins might be the subject of scientific debate but disputed the assertion that the metaphor was redundant based on an as yet unproven clinical hypothesis regarding the persistency of the neurotoxin in the target muscle.

The two largest clinical trials investigating the use of toxins in the symptomatic treatment of cervical dystonia (Benecke *et al*) and blepharospasm (Roggenkamper *et al*) demonstrated equal efficacy and tolerability between Xeomin, which was free from complexing proteins, and Botulinum neurotoxin complex type A (Botox) which was not. A further clinical study had demonstrated no difference in persistence between Xeomin and Botox (Wohlfarth *et al*). No conflicting clinical data challenging equal efficacy, tolerability or persistence had been published to date. Based on this Merz believed that to incorporate non-clinical scientific arguments which were based on a review of data in mice (Aoki *et al*), a preclinical discussion paper (Foster *et al*) and a genetic study of the clostridium bacterium (Johnson and Bradshaw), was misleading and did not present a fair, balanced and clinically relevant view of the matter.

Secondly Allergan stated that Case AUTH/2119/4/08 made comment upon the point that the seed of the horse chestnut did not need its spikey shell to have its effect. This was inaccurate. The case referred to the visual in the context of the claim then at issue 'Neurotoxin you need - complexing proteins you don't' stating that the visual strengthened the impression given by the claim that complexing proteins were unnecessary. As the claim did not appear in any current materials Merz believed that, within the context of this complaint, this ruling was not relevant.

In summary Merz believed that the visual effectively and appropriately supported the headline with which it was associated, namely that Xeomin was 'The first Botulinum neurotoxin free from complexing proteins'. No claim was made or inferred that complexing proteins were not required by, or added value to, other products in the field. Based upon these arguments Merz believed that this was a clear and unambiguous metaphor which reinforced the accurate claim that Xeomin was the first neurotoxin free from complexing proteins and as such contested that the image, with or without the associated text, breached Clause 7.8.

PANEL RULING

The Panel noted its comments above at point 1.

The Panel further noted that the specific role of complexing proteins was the subject of scientific debate as acknowledged by Merz. The Panel considered that associating Xeomin with the horse chestnut visual implied that Xeomin was free of some superfluous, unwanted and possibly injurious element that was otherwise associated with other Botulinum neurotoxins. The Panel considered that the horse chestnut image, and the messages it implied, was misleading. A breach of Clause 7.8 was ruled.

APPEAL BY MERZ

Merz submitted that given the data presented in point 1 above, the visual of the horse chestnut was not in breach of Clause 7.8. The artwork did not mislead as to the nature of the medicine and the image of a chestnut being released from its shell was an appropriate metaphor for the release of Botulinum neurotoxin from its complexing proteins.

Merz did not accept that the visual depicted complexing proteins as 'injurious' (as the spikes on the horse chestnut were soft not hard) but accepted that it might be concluded that complexing proteins were unnecessary and a benefit of clinical significance might be achieved with their removal. Complexing proteins had been demonstrated unnecessary for clinical efficacy and safety to be achieved. They might however impact on product stability and increase the risk for the formation of neutralising antibodies leading to primary or secondary treatment failure. Their removal conferred a clinical advantage of significance. Based on this the visual could be considered a fair and balanced metaphor which did not mislead either directly or indirectly and therefore was not in breach of Clause 7.8.

COMMENTS FROM ALLERGAN

Allergan alleged the image itself was misleading since it was clearly intended to represent the neurotoxin as a smooth and attractive nut and the complexing proteins as a prickly and potentially injurious (rather than soft) outer casing.

As stated above, and as concluded in Case AUTH/2119/4/08, the role of complexing proteins was still the subject of scientific debate. It was thought that the accessory protein might confer an advantage in persistency in the target muscle vs naked neurotoxin (Aoki *et al*; Foster *et al* Johnson and Bradshaw).

Allergan did not agree that the horse chestnut seed and shell was an accurate metaphor for Botulinum toxins. The 'shell' (or complexing proteins) might influence where the 'nut '(or neurotoxin) acted in the target muscle and hence might influence its clinical effect. Merz now stated that the visual might lead the reader to conclude that complexing

proteins were unnecessary and a benefit of clinical significance might be achieved from their removal. Therefore, Allergan alleged that the image was in breach of Clause 7.8.

APPEAL BOARD RULING

The Appeal Board noted its ruling above at point 1. The role of complexing proteins was unclear and the subject of scientific debate. The image implied that the complexing proteins as present in other Botulinum neurotoxins were an unnecessary hazard. The Appeal Board considered that the image and the messages it portrayed were misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.8. The appeal on this point was unsuccessful.

3 Claim 'Low foreign protein load suggests low potential for neutralising antibody formation'

COMPLAINT

Allergan alleged that the claim was misleading and in breach of Clause 7.2 as this observation had not been confirmed in a clinical setting.

As stated above, in a recent Xeomin advertisement in the BMJ, 15 March 2008 (ref 1012a/XEO/NOV/2007), this claim was qualified with the statement 'These observations have not been confirmed in the clinical setting'. A study in rabbits had shown that Xeomin was not associated with any biologically relevant immunogenicity. However, the clinical relevance of this data had yet to be confirmed and long-term use of Xeomin had yet to be investigated (Jost *et al* and Bluemel *et al*).

The two references cited by Merz to support the claim (Jost *et al* and Benecke *et al*) both referred to the animal study undertaken by Merz but also confirmed that clinical studies were required to confirm this observation in an animal model and that 'this issue should be assessed in long-term safety studies with antibody testing' (Benecke *et al*).

Allergan alleged that the claim was misleading, in breach of Clause 7.2.

RESPONSE

Merz noted the allegation that the claim was in breach of Clause 7.2 as it had not been confirmed in a clinical setting. There was no requirement for claims to be purely clinical in Clause 7.2. Clearly the use of rabbit data was of direct relevance to the clinical setting as rabbits had humoral immunity in much the same way as humans. Indeed Allergan's use of animal data to justify its position on complexing proteins above was evidence that it did not hold this view either. Furthermore, although this claim was in the material at issue in Case AUTH/2119/4/08, Allergan did not consider that clinical justification was needed then and did not make this part of its complaint.

Foreign protein, in this case of bacterial origin, injected into humans would produce an immunological effect. This was the basis of human defence from invasion by other biological organisms. Given this fact, the lower the amount of foreign protein the lower the potential for antibody formation.

Xeomin had a very low protein content at 0.6ng/100u (compared with Allergan's Botulinum neurotoxin type A with 5ng/100u for example). Thus with such a low protein load the potential for antibody formation was also low. This had been confirmed with the rabbit study cited in the leavepiece which demonstrated the formation of neutralizing antibodies against Botox treated rabbits (20% of sample) but not against Xeomin treated rabbits (0% of sample) (Bluemel *et al*).

In a clinical setting Jankovic *et al* (2003) directly compared the antibody levels of patients who had been treated with a toxin of 25ng protein/100u with the antibody levels of those on 5ng protein/100u and concluded 'the low risk of antibody formation after current [Botulinum neurotoxin] type A treatment is related to lower protein load' ($p<0.004$). This study was in two preparations of Allergan's Botulinum neurotoxin, but the conclusion was clear.

Unlike the unresolved discussion of the role of complexing proteins in neurotoxin use, the proposition that a low foreign protein load suggested a low potential for neutralizing antibody formation was a matter of scientific consensus and Merz was unaware of any current arguments against this.

Based upon these facts Merz denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that it was an established principle under the Code that all claims related to the clinical situation unless otherwise stated. The supplementary information to Clause 7.2 stated that care must be taken with the use of data derived from *in vitro* studies, studies in healthy volunteers and in animals so as to not mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance.

The Panel noted that the claim at issue was referenced to Jost *et al* which was a review of the pre-clinical and clinical development of Xeomin. A pre-clinical antigenicity study in rabbits suggested that it would be unlikely that therapy would fail

due to antibody formation over long-term use (Bluemel *et al*). Jankovic *et al* had compared the antibody levels produced following the clinical use of two Botulinum neurotoxin type A preparations, one with 25ng protein/100u and the other with 5ng protein/100u. It appeared that extrapolation of those results had led Jost *et al* to state that [Xeomin] was likely to be associated with fewer neutralising antibodies and reduced numbers of secondary non-responders. At the end of their 'discussion' section, Jost *et al* stated that future studies should focus on the administration of Xeomin in Botulinum-A-naive patients, with the aim of investigating its antigenic properties, and determining long-term efficacy and safety profiles.

The Panel noted that although the claim 'Low foreign protein load *suggests* low potential for neutralising antibody formation' (emphasis added) did not directly refer to Xeomin, it was an integral part of the Xeomin leavepiece and was a claim for the product. The Panel did not accept the implication that it would be read as a general scientific proposition. The Panel noted that clinically, the antigenic potential of Xeomin had still to be established. The Panel thus considered that in that regard the claim was misleading as alleged. The use of the word 'suggests' did not negate the impression that a low potential for neutralising antibody formation with Xeomin had been proven. A breach of Clause 7.2 was ruled.

APPEAL BY MERZ

Merz submitted that Schellekens stated that the rabbit data were of direct relevance and significance to the clinical situation (as in point 1). This was also the position taken by the German regulator, BfArM, in the assessment report which stated:

> 'Xeomin (NT 201) contains BoNT/A free of complexing proteins, which undergoes a biological manufacturing process to remove accompanying haemagglutinins. In animal models, Xeomin has shown no detectable immunogenicity. This is anticipated to translate into less neutralising antibodies in patients and fewer secondary non-responders upon longterm therapy.'

Merz submitted that this clearly demonstrated the lower potential of Xeomin to produce neutralising antibodies than either Botox or Dysport. Given this the claim was not misleading and therefore not in breach of Clause 7.2.

COMMENTS FROM ALLERGAN

Allergan alleged that the claim 'Low foreign protein load suggests low potential for neutralising antibody formation' was misleading and in breach of Clause 7.2 as this observation had not been confirmed in a clinical setting. A study in rabbits had shown that Xeomin was not associated with any biologically relevant immunogenicity in this model. However, the clinical relevance of this data had yet to be confirmed and long-term use of Xeomin had yet to be investigated (Jost, *et al*; Bluemel, *et al*).

The statement by Schellekens only supported the argument that there might be a lower potential for Xeomin to produce neutralizing antibodies. He specifically stated that the removal of complexing proteins was 'anticipated' to translate into less neutralizing antibodies.

Therefore, Allergan alleged that this claim was misleading and in breach of Clause 7.2.

APPEAL BOARD RULING

The Appeal Board noted the principle that the greater the amount of foreign protein antigen introduced, the greater the host's antibody response. However, the Appeal Board noted from Allergan that there was evidence that antibodies to the complexing proteins did not affect the efficacy of Botox. The only antibodies that had a neutralising effect were those directed to the core Botulinum neurotoxin itself and more specifically the active site of the molecule. Thus a greater antibody response did not necessarily mean that there would be an increase in neutralizing antibodies.

The Appeal Board noted that although the claim 'Low foreign protein load *suggests* low potential for neutralising antibody formation' (emphasis added) did not directly refer to Xeomin, it was an integral part of the Xeomin leavepiece and was a claim for the product. The Appeal Board noted that rabbit data from Bluemel *et al* had suggested that Xeomin use was not associated with the formation of neutralising antibodies. The assessment report for Xeomin prepared by the German regulator, BfArM, referred to anticipated less neutralising antibodies. The expert opinion provided by Merz stated that the reduced immunogenicity in rabbits might be extrapolated to patients. There was no mention of neutralising antibodies nor was it clear whether the expert had introduced an element of caution with regard to extrapolation to patients or had, in effect, given permission to extrapolate (as interpreted by Merz). However, the Appeal Board noted that clinically the antigenic potential of Xeomin had still to be established. The Appeal Board considered that the claim was misleading and it upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

4 Implied breach of undertaking

As stated above, this aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

RESPONSE

Merz noted that the claim found in breach in Case AUTH/2119/4/08 was 'Neurotoxin you need - complexing proteins you don't'. The Panel ruling stated 'The Panel considered that the claim was misleading'. The claim had been withdrawn and had not been used again. The visual was only mentioned in the sense that it strengthened the claim. The visual was not the subject of the complaint and therefore was not ruled upon by the Panel.

Merz had complied fully with the undertaking and had not reused the claim at issue. Merz denied that it had breached Clauses 2, 9.1 and 25.

PANEL RULING

The Panel noted that in the previous case, Case AUTH/2119/4/08, Allergan had complained about the claim 'Neurotoxin you need – complexing protein you don't'. The Panel had considered the claim in association with the image of the horse chestnut emerging from its spiky shell. The Panel, *inter alia*, considered that the claim implied a proven clinical disadvantage for those Botulinum neurotoxin type A products associated with complexing proteins for which there was no supporting data. The impression was strengthened by the picture of the chestnut (the neurotoxin) and its spiky shell (the complexing proteins). The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted its comments and ruling in point 1 above and considered that the messages conveyed in the leavepiece now at issue were closely similar to those considered in Case AUTH/2119/4/08 and were covered by the undertaking given in that case. Given that the leavepiece implied a clinical disadvantage for Botulinum neurotoxins with complexing proteins, the Panel considered that Merz had not complied with its undertaking. A breach of Clause 25 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel considered that in breaching its undertaking Merz had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

APPEAL BY MERZ

Merz submitted that in the ruling in point 1 the Panel stated that the claim was different to that at issue in Case AUTH/2119/4/08 and went on to state that the claim was a statement of fact, which the original claim was not. The claim now at issue was different, had a different meaning, and was factual. The Panel's statement that it was 'different' and 'closely similar' were contradictory. The original claim was withdrawn and not reused.

Merz submitted that 'free from complexing proteins' was an SPC statement, chosen for its unambiguity and it was a regulatory approved referenced statement. Totally different from the prior case it was not from opinion or peer reviewed literature that was identified in the prior ruling as being 'still for scientific debate'.

Merz submitted that the Panel asserted that the claim should be assessed within the context of the associated visual. The visual of the horse chestnut emerging from its shell had not been the subject of the previous complaint and ruling, and had been integral to the campaign since its launch.

Merz noted that in Cases AUTH/1588/5/04 and AUTH/1589/5/04 Bristol-Myers Squibb and Sanofi-Synthelabo were found not to have breached an undertaking. The claim at issue was: 'Imagine you've had a heart attack, stroke or have PAD, Imagine you've been prescribed aspirin, imagine improving on that. Plavix delivers significant protection above and beyond aspirin'. It was found in breach of Clauses 7.2 and 7.4 as 'the implied claim for benefit compared to aspirin could not be substantiated' as 'the study was not powered to evaluate efficacy in individual subgroups'. The two companies were also asked to answer the allegation of a breach of undertaking issued after Case AUTH/889/6/99. The advertisement claimed that: 'compared to aspirin, Plavix was significantly more effective at reducing MI, reducing stroke and reducing vascular death'. In this case the claim was found to be misleading and breach was ruled. The associated breach of undertaking was ruled by the Panel to be 'not so' as 'the study was powered to detect a realistic treatment effect in the whole study cohort and not each of the three clinical subgroups'. The Panel's view was that there was no breach of undertaking despite the almost identical wording of the claims and identical Panel rulings.

Merz submitted that there was clear inconsistency in the rulings of the Panel if the Xeomin claim, which was acknowledged by the Panel to be different to that at issue in Case AUTH/2119/4/8 and a statement of fact, was found in breach of undertaking when a claim that was almost identical had historically not been found in breach.

Merz submitted that the claim was sufficiently different not to be a breach of undertaking as it was acknowledged as different by the Panel and finding this in breach would create a contradiction in the Panel's rulings.

Merz submitted that the ruling that the claim was in breach of undertaking was clearly incorrect and ran against precedent set by the Panel. There had

been no breach of undertaking and Merz had continued to maintain high standards and not engage in promotional activity likely to bring discredit upon the industry. The ruling of breaches of Clauses 25, 9.1 and 2 must be overturned.

COMMENTS FROM ALLERGAN

Allergan had not complained about a possible breach of undertaking and thus it did not have the right to comment on Merz's appeal.

APPEAL BOARD RULING

The Appeal Board noted that in Case AUTH/2119/4/08 Allergan had complained about the claim 'Neurotoxin you need – complexing protein you don't'. The Panel had considered the claim in association with the image of the horse chestnut emerging from its spiky shell. The Panel, *inter alia*, considered that the claim implied a proven clinical disadvantage for those Botulinum neurotoxin type A products associated with complexing proteins for which there was no supporting data. The impression was strengthened by the picture of the chestnut (the neurotoxin) and its spiky shell (the complexing proteins). The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

The Appeal Board considered that the claim at issue 'The first Botulinum neurotoxin free from complexing proteins' was different to the claim at issue in Case AUTH/2119/4/08 'Neurotoxin you need – complexing protein you don't'. The Appeal Board noted that the image of the horse chestnut accompanying both claims was the same. There had been no ruling specifically related to the image in Case AUTH/2119/4/08. The Appeal Board noted that Merz had taken steps to comply with its undertaking given in Case AUTH/2119/4/08. The Appeal Board did not consider that the current material meant that Merz had breached its undertaking and no breach of Clause 25 was ruled. Consequently the Panel's rulings of breaches of Clauses 9.1 and 2 no longer stood. The appeal on this point was successful.

Complaint received **20 October 2008**

Case completed **16 February 2009**

GENUS v STIEFEL LABORATORIES

Alleged inappropriate rebate

Genus complained about the marketing of Oilatum Cream by Stiefel Laboratories. Genus supplied Cetraben.

Genus stated that it received an email on 13 October from a primary care trust (PCT), stating that Stiefel had offered the PCT a rebate on the price difference between Cetraben and Oilatum if the PCT reinstated Oilatum onto the PCT formulary. Genus alleged that this not only breached the Code but more seriously was an inducement to prescribe which discredited and reduced confidence in the industry.

The detailed response from Stiefel Laboratories is given below.

The Panel noted that the supplementary information to the Code stated that 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 were outside the scope of the Code. Other trade practices were subject to the Code. The terms 'prices', 'margins' and 'discounts' were primarily financial terms. The Panel considered that a cash rebate scheme was related to prices, margins and discounts. However, it did not know whether such schemes were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993. Stiefel had not provided any information in this regard. Thus the matter now at issue had to be considered as its exemption from the Code had not been established.

The Panel noted the parties' account of events differed. The complaint was based upon the following from a third party: 'I have been contacted by Steefel [sic] and they are going to give us a rebate on the prescription if we put back oilutim [sic] on the formulary, I am considering, you asked me to let you know'. Thus according to the third party, Stiefel had offered the rebate to the local PCT if it reinstated Oilatum onto its formulary. Stiefel's account of the matter was that the local PCT indicated that if Stiefel arranged a rebate scheme for Oilatum then Cetraben would be taken off the formulary. The question was, did Stiefel offer the cash rebate in exchange for reinstatement of its product onto the formulary or did the PCT ask for the rebate and offer reinstatement? The Panel noted Stiefel's submission that no agreement was made regarding any rebate scheme and the discussions which had taken place with the PCT were information sharing only.

The Panel considered that given the parties' differing accounts it was not possible to establish, on the balance of probabilities, what had actually occurred. No breach of the Code was thus ruled.

Genus Pharmaceuticals Ltd complained about the marketing of Oilatum Cream by Stiefel Laboratories (UK) Limited. Genus supplied Cetraben.

COMPLAINT

Genus regretted that, following written dialogue with Stiefel concerning a serious breach of Clauses 18.1 and 2 of the Code in relation to the marketing of Oilatum, it had no further option other than to complain to the Authority.

Genus stated that it received an email on 13 October from a primary care trust (PCT) stating that Stiefel had offered the PCT a rebate on the price difference between Cetraben and Oilatum if the PCT reinstated Oilatum onto the PCT formulary. Genus alleged that this not only breached Clause 18.1 but more seriously was an inducement to prescribe which discredited and reduced confidence in the industry.

Genus wrote to Stiefel requesting its response concerning this serious issue; the response then denied any breach of Clauses 18.1 and 2. Genus then emailed Stiefel to state that following its response, Genus would refer its complaint to the Authority. Stiefel had requested a copy of the email sent to Genus by the PCT but as this was private correspondence, it was considered inappropriate to divulge the author's identity. However Genus confirmed to Stiefel that the wording of its charge accurately reflected the text of the PCT correspondence.

RESPONSE

Stiefel Laboratories stated that it was saddened by Genus's action especially after several attempts were made to talk directly with the company to better understand its concerns and respond appropriately. Stiefel did not believe that any action that it had taken had breached the Code and certainly not in respect of Clauses 18.1 and 2, hence being totally surprised by Genus' accusations.

The series of events referred to by Genus were as follows. Stiefel understood that a number of pharmaceutical companies operated cash rebate schemes. To understand if such could be applied to Stiefel and its product portfolio, a meeting was organised on 7 October at the PCT headquarters.

In these discussions, the agenda and objectives for both parties were two-fold: an exploration as to how recent National Institute for Health and Clinical Excellence (NICE) guidelines on atopic dermatitis could be disseminated across the trust with educational initiatives and a discussion of local rebate schemes employed by either the PCT or the local hospital. This was a follow up to previous brief discussions with PCT pharmaceutical advisors at a PCT meeting held in central London in July 2008.

No arrangements were made with either party to undertake a rebate scheme for Oilatum Cream but the different schemes that the PCT currently operated were highlighted, one of which was with Genus for its product Cetraben. The PCT indicated that, if Stiefel wished to arrange a particular rebate scheme, the incumbent (ie Cetraben) would be taken off the current rebate scheme. Stiefel reiterated that no agreements were made to enter into any rebate scheme and that the discussions were information sharing only. The PCT could confirm these series of events and the exact nature of the discussions.

* * * * *

The Authority also received a letter from the PCT but as it had not been sent with Stiefel's authority it could not form part of Stiefel's response. It was thus not considered by the Panel.

PANEL RULING

The Panel noted that the supplementary information to Clause 18.1, Terms of Trade, stated that 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 were outside the scope of the Code. Other trade practices were subject to the Code. The terms 'prices', 'margins' and 'discounts' were primarily financial terms. The Panel considered that a cash rebate scheme was related to prices, margins and discounts. However, it did not know whether such schemes were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993. Stiefel had not provided any information in this regard. Thus the matter now at issue had to be considered as its exemption from the Code had not been established.

The Panel noted the parties' account of events differed. The complaint was based upon the following from a third party: 'I have been contacted by Steefel [sic] and they are going to give us a rebate on the prescription if we put back oilutim [sic] on the formulary, I am considering, you asked me to let you know'. Thus according to the third party, Stiefel had offered the rebate to the local PCT if it reinstated Oilatum onto its formulary. Stiefel's account of the matter was that the local PCT indicated that if Stiefel arranged a rebate scheme for Oilatum then Cetraben would be taken off the formulary. The question was, did Stiefel offer the cash rebate in exchange for reinstatement of its product onto the formulary or did the PCT ask for the rebate and offer reinstatement? The Panel noted Stiefel's submission that no agreement was made regarding any rebate scheme and the discussions which had taken place with the PCT were information sharing only.

The Panel considered that given the parties' differing accounts it was not possible to establish, on the balance of probabilities, what had actually occurred. No breach of Clause 18.1 was thus ruled. It thus followed that there could be no breach of Clause 2.

Complaint received **6 November 2008**

Case completed **27 January 2009**

CASE AUTH/2183/11/08

MERZ PHARMA v ALLERGAN

Botox representative activity

Merz Pharma complained about the activities of Allergan representatives in relation to the promotion of Botox (botulinum toxin). Merz supplied Xeomin (also botulinum toxin).

Merz stated that following the Toxins Conference in Italy in June physicians reported that Allergan representatives were stating that Xeomin was only 70% as potent as Botox. This was confirmed on 1 October by a named health professional, who told a Merz representative that an Allergan representative had claimed that the dosing ratio of Xeomin to Botox was 0.7:1.

At the Toxins Conference Allergan published a poster suggesting that, based upon an Allergan test of potency on three vials of Xeomin, the potency of Xeomin was considerably less than that of Botox (Brown *et al* 2008). This animal study clearly did not agree with the two largest clinical trials conducted with Xeomin vs Botox (Jankovic 2003, Benecke *et al* 2005), other animal data presented at the meeting (Dressler 2008) or the summaries of product characteristics (SPCs) for the two products that had identical dosing regimens.

Merz knew that directly following this conference Allergan representatives had a two day training meeting. It was after this training that Merz received reports from the field about the claim of lower potency.

Merz explained that due to the toxicity of botulinum toxins, European regulators had issued a 'Dear Doctor' letter in 2007 warning health professionals about their potential systemic toxic effects and strongly advising them not to exceed the recommended dose. Clearly Allergan representatives telling health professionals that Xeomin was less potent might lead health professionals to overdose patients by up to 40% with Xeomin. Merz was very concerned that this activity could compromise patient safety.

The fact that communication of these data was part of the wider corporate communications strategy of Allergan was further reinforced with the reprinting and distribution of a poster entitled 'Substandard potency of Xeomin in the Botox mouse LD_{50} assay' at the recent European Dystonia Federation (EDF) Meeting held in Germany in October. The poster (Hunt and Clarke 2006) detailed an Allergan study and stated the potency of Xeomin at 69% of that of Botox; it was offered by representatives and was freely available from the display rack of the promotional stand at this meeting. Merz picked up several copies. In Allergan's response to Merz's concerns it stated explicitly that it had 'vigorously argued against' the use of fixed ratios citing 'regulatory approvals across Europe'. This was at odds with the activity that took place at Dystonia Europe and the multiple reports that Merz had received from customers.

Such activity by Allergan representatives was inaccurate, misleading and did not lead to the rational use of either Botox or Xeomin. As reports of this activity started following a two day briefing meeting Merz concluded that the representatives were provided with and briefed on this data, which was contrary to both SPCs. Breaches of the Code were alleged.

In Case AUTH/2117/4/08 Allergan successfully challenged Merz using direct comparison of toxin doses. Thus Allergan's current activity showed a disregard for the Authority's rulings and potentially compromised patient safety; it was a failure to maintain high standards and a promotional activity likely to bring discredit upon the industry in breach of the Code including Clause 2.

The detailed response from Allergan is given below.

The Panel examined the material provided by Allergan. It noted Merz' allegation that an Allergan representative had claimed that the dosing ratio of Xeomin to Botox was 0.7:1. At a conference in Italy Allergan had published a poster based on an Allergan test of potency of three vials of Xeomin (Brown *et al*). The poster was headed 'Xeomin displays lower potency and is neutralized by anti-Botox antibodies'. This concluded that in a mouse assay with lower potency and similar antigenicity, Xeomin was not dose-equivalent to Botox.

At a conference in Germany Allergan had distributed a poster (Hunt and Clarke) entitled 'Substandard Potency of Xeomin in the Botox Mouse LD_{50} Assay'. The poster concluded that the potencies of three lots of Xeomin were substantially lower than the labelled 100U/vial when tested in the Botox LD_{50} mouse assay and that the results confirmed that the potency of Xeomin was not equivalent to that of Botox.

Merz referred to Dressler presented at the same meeting as Brown *et al*. Dressler was headed 'Equivalent Potency of Xeomin and Botox' and concluded from 5 batches of Xeomin and Botox using the LD_{50} bioassay that the biological potencies of Xeomin and Botox were equivalent. It further stated that conversions could be performed at a 1:1 conversion ratio allowing easy exchange of both medicines in a therapeutic setting.

The Panel noted that the Botox SPC stated that botulinum toxin units were not interchangeable from one product to another. The Xeomin SPC stated due to differences in the LD_{50} assay these units were specific to Xeomin and were not interchangeable with other botulinum toxin preparations.

The Panel noted that Allergan UK stated that it did not hold any promotional activities at the two European meetings nor did it sponsor physicians to attend. There were Allergan stands at both meetings. It was not clear whether Allergan UK had held non promotional activities at the meetings. However in the Panel's view the complaint concerned the conduct of representatives in the UK and not the European meetings.

The Panel examined the materials provided by Allergan. The product monograph was dated November 2007. Page 18 compared enzymatic activity results between Botox and Xeomin. The test referred to Hunt and Clarke and their findings that 100 Xeomin units were not equivalent to 100 Botox units and that Xeomin showed substantially lower potency than the Botox reference standard. This section made it clear that the products should not be interchanged in clinical practice since it was not possible to apply a simple conversion factor and it was not recommended to attempt to fix a dose ratio. Reference was also made to the SPC statements that biological units were not applicable to any other product. The product monograph also recommended that physicians gained experience with one or more formulations and avoided changing patients between formulations wherever possible unless this was the only option for successful treatment. The product monograph concluded that there were clear differences between, *inter alia*, Botox and Xeomin in terms of potency and migration. As such there was no comparability between the different preparations and it was not possible to establish a dose ratio conversion since none of the products were interchangeable.

The Allergan competitor update presentation in May 2008 included a graph showing a light-chain activity kinetic comparison of Botox and Xeomin in which the activity of Botox appeared to be twice that of Xeomin. This was referenced to data on file. Within an SPC comparison section a slide headed 'Botox v Xeomin' included the bullet points 'Potency', 'Safety', Lack of data' and 'Licensed indications' but no further details were given.

The detail aid did not compare the products. The objection handler (dated October 2007 and according to Allergan put on hold until February 2008) included information about Xeomin. One page was headed 'Botox and Xeomin do not have equivalent potency' referenced to Hunt and Clarke. A bar chart comparing average corrected potency (Botox LD_{50} units per vial) showed Botox at 95 and Xeomin at 69, 75 and 78. Adjacent to the bar chart was the claim 'The potencies of the 3 unexpired lots of Xeomin were substantially lower than Botox when tested in the Botox mouse LD_{50} assay'.

The Panel considered that given the comparative potency information in the product monograph and the objection handler it was not unrealistic that representatives might have used this information when promoting Botox to health professionals. There was no instruction about how to use the information comparing the potency of Xeomin and Botox. The Panel considered that on the balance of probabilities Allergan's representative had claimed there was a difference in potency for the products. This was inconsistent with the SPCs which had similar dosing regimens for the products. The Panel accepted there was some animal data that possibly showed a difference. However the supplementary information to the Code was clear that animal data should not be extrapolated to the clinical situation unless there was data to show it was of direct relevance and significance. This had not been demonstrated. The Panel considered that the product monograph and the objection handler were misleading with regard to the information about potency. The comparison could not be substantiated and did not reflect all the evidence. The material would not encourage the rational use of a medicine. Thus the Panel ruled breaches of the Code. The Panel considered that as the briefing material did not comply with the Code there was also a breach in that regard. The Panel considered that high standards had not been maintained and a breach was ruled. 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.

Merz Pharma UK Ltd complained about the activities of Allergan Ltd representatives in relation to the promotion of Botox (botulinum toxin). Merz supplied Xeomin (also botulinum toxin).

COMPLAINT

Merz stated that following the Toxins Conference in Baveno, Italy (12-15 June) physicians reported that Allergan representatives were stating that Xeomin was only 70% as potent as Botox. This was confirmed on 1 October by a named health professional, who told a Merz representative that an Allergan representative had claimed that the dosing ratio of Xeomin to Botox was 0.7:1.

At the Toxins Conference Allergan published a poster suggesting that, based upon an Allergan test of potency on three vials of Xeomin, the potency of Xeomin was considerably less than that of Botox (Brown *et al* 2008). This animal study clearly did not agree with the two largest clinical trials conducted with Xeomin vs Botox (Jankovic 2003, Benecke *et al* 2005), other animal data presented at the meeting (Dressler 2008) or summaries of product characteristics (SPCs) for the two products that had identical dosing regimens.

Merz knew that directly following this conference Allergan representatives had a two day training meeting. It was after this training that Merz received reports from the field about the claim of lower potency.

Botulinum toxins were the most toxic substance known to man and had been the subject of a European Medicines Agency Pharmacovigilance Working Party in 2007 that resulted in a 'Dear Doctor' letter being issued. This letter warned about the potential systemic toxic effects of toxins and strongly advised health professionals not to exceed the recommended dose. Clearly Allergan representatives telling health professionals that Xeomin was less potent might lead health professionals to overdose their patients by up to 40% with Xeomin. It was possible therefore that this activity could compromise patient safety. This gave Merz great cause for concern.

The fact that communication of these data was part of the wider corporate communications strategy of Allergan was further reinforced with the reprinting and distribution of a poster entitled 'Substandard potency of Xeomin in the Botox mouse LD_{50} assay' at the recent European Dystonia Federation (EDF) Meeting held in Hamburg, 17-19 October. The poster (Hunt and Clarke 2006) detailed and Allergan study and stated the potency of Xeomin at 69% of that of Botox; it was offered by representatives and was freely available from the display rack of the promotional stand at this meeting. Merz personnel picked up several copies. In Allergan's response to Merz's concerns it stated explicitly that it had 'vigorously argued against' the use of fixed ratios citing 'regulatory approvals across Europe'. This was at odds with the activity that took place at Dystonia Europe and the multiple reports that Merz had received from customers including verbal communications and slide presentations.

Such activity by Allergan representatives was inaccurate, misleading, and did not lead to the rational use of either Botox or Xeomin. Breaches of Clauses 7.2, 7.3 and 7.10 of the Code were alleged.

As reports of this activity started following a two day briefing meeting Merz concluded that the representatives were provided with and briefed on this data, which was contrary to both SPCs. A breach of Clause 15.9 was alleged.

In Case AUTH/2117/4/08 Allergan successfully challenged Merz using direct comparison of toxin doses. Thus Allergan's current activity showed a disregard for the Authority's rulings and potentially compromised patient safety; it was a failure to maintain high standards and a promotional activity likely to bring discredit upon the industry in breach of Clauses 9.1 and 2.

Whilst it was not possible for Merz to have access to the training or other materials issued to Allergan representatives the chronology of the activity and the specificity of the information provided by the health professional and others were convincing enough for Merz to have little doubt that this activity took place.

Merz had made every effort to resolve this dispute. Allergan had rejected Merz's request that it brief its sales force on the respective SPC guidance for both products given the potential patient safety issues.

Allergan had been informed of Merz's intention to proceed to a formal complaint.

RESPONSE

Allergan welcomed the opportunity to respond to the allegations raised by Merz and had tried to tease out the various issues raised in its letter. Some of the issues raised seemed to be new and were not the subject of the earlier correspondence.

1 Initial complaint regarding a representative and alleged briefing document to the sales force

As could be seen from the inter-company dialogue the thrust of the initial complaint from Merz related to alleged activities by a single representative and the belief that a briefing had been sent to the sales force to support or encourage the representative in these activities.

Allergan responded to the initial complaint and, when provided with the details of the representative involved, fully investigated the allegations. Allergan confirmed on 31 October that the representative had not, and was not, using any confidential Merz sales data as alleged. On a wider point, Allergan reassured Merz that it had not briefed its sales representatives to disparage Xeomin or Merz, nor had it supplied any materials to support such an activity.

Therefore, on this specific issue Allergan strongly denied the alleged breaches of Clauses 7.2, 7.3, 7.10, 15.9, 9.1 and 2.

2 Alleged patient safety issue and request to issue a briefing to the Allergan sales force

On the wider issue of patient safety, Allergan took very seriously any concerns regarding patient safety. It confirmed that its representatives did not have any materials that promoted a dosing ratio of 0.7:1 or any other fixed ratio. Indeed any use of a fixed dose ratio for any of the botulinum toxins was something Allergan had vigorously argued against with competitors for many years and would continue to clarify this position with clinicians if they were in any doubt on this issue.

Accordingly, Allergan did not believe there were any grounds to request that it issue any briefing on this matter to its sales representatives.

Allergan had not engaged in any activity which showed a disregard for the ruling of the Authority, potentially compromised patient safety or had not maintained high standards. Allergan strongly refuted the alleged breaches of Clause 9.1 or 2.

3 Toxins 2008 Conference in Baveno, Italy and alleged two day training meeting

Allergan was unclear as to why the Toxins Conference had been raised at this juncture and the relevance to this complaint. Allergan UK did not sponsor any physicians to attend the conference and nor did Allergan UK hold any promotional activities at the meeting.

A number of UK physicians would have attended as this was one of the major conferences for specialists working with botulinum toxins. Indeed, Allergan believed a number of UK physicians were sponsored by Merz to attend.

There was a full scientific programme at the meeting and 158 abstracts were presented. During the conference there was a scientific session at which each of the companies which marketed a botulinum toxin (Merz, Allergan, Ipsen and Solstice) presented scientific data on their respective products. This session produced considerable debate about the question of interchangeability and the different properties of the different botulinum toxin products. It was most likely that genuine legitimate scientific exchange at this conference had raised the comparison of the two products and interest in the range of data published on the products including the abstracts by both Brown *et al* and Dressler.

Following the Toxins Conference, Merz had alleged that 'the Allergan representatives had a two day training meeting'. Allergan confirmed that no such meeting for Allergan UK representatives took place.

4 European Dystonia Federation (EDF) Meeting 2008, Hamburg, Germany

Allergan was unclear why the EDF Meeting had been raised at this juncture and the relevance to this complaint. Allergan UK did not sponsor any physicians to attend the conference and nor did Allergan UK hold any promotional activities at the meeting.

There was a full scientific programme at the meeting. It was most likely that genuine legitimate scientific exchange at this conference, and others, had raised the comparison of the two products and interest in the range of published data including the abstract by Hunt and Clarke.

Overall, this entire complaint was based on supposition and allegation with no direct supporting evidence.

In conclusion, Allergan strongly denied the alleged breaches of Clauses 7.2, 7.3, 7.10, 15.9, 9.1 or 2.

FURTHER RESPONSE

Following a request for further information Allergan provided copies of material used by the representatives in the last six months to promote Botox. These being:

- An SPC comparison document
- Presentation slides from a competitor update session held at the UK Neurosciences Sales Meeting 14-15 May 2008. Following release of the objection handler to the sales force, training on its use was undertaken via workshops and role play. It was designed for reactive use only and was not a key part of the T2 campaign. The T2 training session campaign implementation presentation and workbook used at the meeting were also provided although there was no specific mention of Xeomin in these documents.
- At the subsequent UK Neurosciences Sales Meeting (10-12 September 2008) the focus was again on delivering the core Botox campaign – 'right muscles' and 'right dose'. The first day focussed on workshop training provided by an external expert and professor of rehabilitation medicine. The second day focussed on selling skills. There were no sessions or briefings provided on Xeomin.

The sales representatives had not been given copies of Brown *et al* or Hunt and Clarke. Data taken from Hunt and Clarke was included in the certified objection handler and in the certified product monograph.

PANEL RULING

The Panel examined the material provided by Allergan. It noted Merz' allegation that an Allergan representative had claimed that the dosing ratio of Xeomin to Botox was 0.7:1. At a conference in Italy Allergan had published a poster based on an Allergan test of potency of three vials of Xeomin (Brown *et al*). The poster was headed 'Xeomin displays lower potency and is neutralized by anti-Botox antibodies'. This concluded that in a mouse assay with lower potency and similar antigenicity, Xeomin was not dose-equivalent to Botox.

At a conference in Germany Allergan had distributed a poster (Hunt and Clarke) entitled 'Substandard Potency of Xeomin in the Botox Mouse LD_{50} Assay'. The poster concluded that the potencies of three lots of Xeomin were substantially lower than the labelled 100U/vial when tested in the Botox LD_{50} mouse assay and that the results confirmed that the potency of Xeomin was not equivalent to that of Botox.

Merz referred to Dressler presented at the same meeting as Brown *et al*. Dressler was headed 'Equivalent Potency of Xeomin and Botox' and

concluded from 5 batches of Xeomin and Botox using the LD_{50} bioassay that the biological potencies of Xeomin and Botox were equivalent. It further stated that conversions could be performed at a 1:1 conversion ratio allowing easy exchange of both medicines in a therapeutic setting.

The Panel noted that the Botox SPC stated that botulinum toxin units were not interchangeable from one product to another. The Xeomin SPC stated that due to differences in the LD_{50} assay these units were specific to Xeomin and were not interchangeable with other botulinum toxin preparations.

The Panel noted that Allergan UK stated that it did not hold any promotional activities at the two European meetings nor did it sponsor physicians to attend. There were Allergan stands at both meetings. It was not clear whether Allergan UK had held non promotional activities at the meetings. However in the Panel's view the complaint concerned the conduct of representatives in the UK and not the European meetings.

The Panel examined the materials provided by Allergan. The product monograph (Ref ACA/0343/2007/UK) was dated November 2007. Page 18 compared enzymatic activity results between Botox and Xeomin. The test referred to Hunt and Clarke and their findings that 100 Xeomin units were not equivalent to 100 Botox units and that Xeomin showed substantially lower potency than the Botox reference standard. This section made it clear that the products should not be interchanged in clinical practice since it was not possible to apply a simple conversion factor and it was not recommended to attempt to fix a dose ratio. Reference was also made to the SPC statements that biological units were not applicable to any other product. The product monograph also recommended that physicians gained experience with one or more formulations and avoided changing patients between formulations wherever possible unless this was the only option for successful treatment. The product monograph concluded that there were clear differences between, *inter alia*, Botox and Xeomin in terms of potency and migration. As such there was no comparability between the different preparations and it was not possible to establish a dose ratio conversion since none of the products were interchangeable.

The Allergan competitor update presentation in May 2008 included a graph showing a light-chain activity kinetic comparison of Botox and Xeomin in which the activity of Botox appeared to be twice that of Xeomin. This was referenced to data on file. Within an SPC comparison section a slide headed 'Botox v Xeomin' included the bullet points 'Potency', 'Safety', Lack of data' and 'Licensed indications' but no further details were given.

The detail aid did not compare the products. The objection handler (ACA/1303/2006 dated October 2007 and according to Allergan put on hold until February 2008) included information about Xeomin. One page was headed 'Botox and Xeomin do not have equivalent potency' referenced to Hunt and Clarke. A bar chart comparing average corrected potency (Botox LD_{50} units per vial) showed Botox at 95 and 3 lots of Xeomin at 69, 75 and 78. Adjacent to the bar chart was the claim 'The potencies of the 3 unexpired lots of Xeomin were substantially lower than Botox when tested in the Botox mouse LD_{50} assay'.

The Panel considered that given the comparative potency information in the product monograph and the objection handler it was not unrealistic that representatives might have used this information when promoting Botox to health professionals. There was no instruction about how to use the information comparing the potency of Xeomin and Botox. The Panel considered that on the balance of probabilities the Allergan representative had claimed there was a difference in potency for the products. This was inconsistent with the SPCs which had similar dosing regimens for the products. The Panel accepted there was some animal data that possibly showed a difference. However the supplementary information to Clause 7.2 was clear that animal data should not be extrapolated to the clinical situation unless there was data to show it was of direct relevance and significance. This had not been demonstrated. The Panel considered that the product monograph and the objection handler were misleading with regard to the information about potency. The comparison could not be substantiated and did not reflect all the evidence. The material would not encourage the rational use of a medicine. Thus the Panel ruled breaches of Clauses 7.2, 7.3 and 7.10.

The Panel considered that as the briefing material did not comply with the Code there was also a breach of Clause 15.9.

The Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled. 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.

Complaint received **13 November 2008**

Case completed **28 January 2009**

GENERAL PRACTITIONER v PROSTRAKAN

Provision of a service

A senior partner in a two-handed GP practice complained that his partner and a receptionist had authorised ProStrakan to carry out a survey and that that company was given a list of the patients for it to write to direct and whoever did the survey also wrote [Adcal-D_3] which was promoted and made by ProStrakan.

The detailed response from ProStrakan is given below.

The Panel noted that the complainant firstly queried whether appropriate signatories had been obtained for the Practice Authorisation Form. That dated 6 May 2008 jointly listed the complainant and his partner as the lead GP and the second signatory as the practice manager. The declaration on the form read 'We hereby authorise [the agency] to undertake the Calcium and Vitamin D supplementation project and will inform all partners of this agreement. We are duly authorised to sign this form on behalf of the practice', beneath which the complainant's partner alone signed as the lead GP and the second signatory was the practice manager. The form subsequently signed on 21 July did not mention the complainant; his partner alone was listed as lead GP and signed as such alongside the practice manager.

The Panel noted that the Calcium and Vitamin D Supplementation Clinical Review Protocol required the practice authorisation form to be completed and signed by an authorised independent prescriber and the practice manager prior to any work being undertaken. ProStrakan explained that representatives were instructed to discuss the protocol in detail during a non-promotional call and ensure that any objections had been dealt with. Identification of lead GPs and their approval was dealt with during the detailed discussion of the protocol. In addition ProStrakan explained that the pharmacist from the agency was instructed to check the authorisation form to ensure that all relevant sections were complete and signed by a lead GP and to ensure practice understanding of the service. According to ProStrakan on neither 6 May nor 21 July did practice staff raise issues or concerns regarding either the signatories' authority or the awareness of other partners and the practice of the service.

The Panel noted that the complainant, the senior GP partner, was concerned that the service had been completed without his authorisation. The Panel noted ProStrakan's submission that neither the company nor its agents were responsible for determining whether a medical professional who signed as a lead GP was indeed the lead GP or verifying that signatories had abided by their commitment to inform all partners of the agreement to implement a therapy review. The Panel considered, however, that there might be circumstances where further enquiries about such matters ought to be made. The Panel queried whether the representative and pharmacist should have sought the complainant's view given the reference to him on the first form. The Panel noted however that he had not signed the declaration on the first form. The declaration placed the responsibility on the signatories to inform '… all partners of this agreement'.

ProStrakan had submitted that on 21 July the practice staff raised no concerns or issues regarding the authorisation of the therapy review. The Panel considered that whilst it was impossible to determine exactly what had transpired at the practice it had insufficient evidence to indicate that the service had not been authorised as required by the protocol. The Panel considered that although it might have been prudent to obtain the complainant's signature, failure to do so, given the declaration signed by his partner, did not mean that high standards had not been maintained. No breach of the Code was ruled.

The Panel noted that the service was run by an agency on behalf of ProStrakan. The protocol provided that ProStrakan played no role in the service provision other than reimbursement of the service provider. ProStrakan did not receive a list of practices or any patient details or have any patient contact. The pharmacist wrote to patients in accordance with the agreed protocol. There was no evidence before the Panel that ProStrakan had received patient data and/or written to patients as alleged. No breach of the Code was ruled.

The Panel noted the complainant's allegation that whoever did the survey also wrote ProStrakan's medicine. The Panel noted that any change in medicine as a result of the service had to be agreed by the lead doctor. The Panel considered that it did not have an allegation about whether the service was acceptable, as the complainant had made no specific comment in this regard. The Panel noted that pharmaceutical companies could provide medical and educational goods and services, including therapy review programmes, but these needed to comply with the Code. It was not necessarily a breach of the Code for products from the company providing the service to be prescribed. Taking all the circumstances into account the Panel decided in relation to the complainant's allegation that there was no breach of the Code.

A general practitioner complained about a calcium

and vitamin D_3 service run by ProStrakan Group plc. ProStrakan provided Adcal-D_3, a calcium and vitamin D_3 supplement.

COMPLAINT

A senior partner in a two-handed GP practice, complained that his partner and a receptionist had signed papers authorising ProStrakan to carry out a survey and that that company was given a list of the patients for it to write to direct and whoever did the survey also wrote [Adcal-D_3] which was promoted and made by ProStrakan.

When writing to ProStrakan the Authority asked it to respond in relation to Clauses 2, 9.1 and 18.1 of the Code.

RESPONSE

ProStrakan explained that on 6 May the practice was visited by two therapy review pharmacists from its agent. There appeared to have been a mix-up however, since the practice staff were unaware that the visit was to occur. The complainant's partner and the practice manager signed the protocol agreement. However, the therapy review did not occur on that occasion as the practice was not prepared and requested that the review be performed at a later date. An appointment was made for 21 July. Once again, the protocol was signed by the complainant's partner and the practice manager and the therapy review was implemented on that date.

ProStrakan noted the original protocol dated 6 May listed two GPs as 'lead'. The second protocol listed the complainant's partner as lead GP. He signed as lead GP on both occasions. Section 1 of the protocol signed 21 July stated 'We hereby authorise [the agency] to undertake the calcium and vitamin D_3 Deficiency Clinical Review and will inform all partners of this agreement. We are duly authorised to sign this form on behalf of the practice'. [the authorisation form dated 6 may described the service as 'The Calcium and Vitamin D Supplementation Project']. The complainant's partner signed this section of the protocol agreement. ProStrakan and its agents were not responsible for determining whether a medical professional who signed as a lead GP was indeed the lead GP for that practice, particularly when the form indicated that that individual was a lead GP. By the same token, ProStrakan and its agents were not responsible for verifying that signatories had abided by their commitment to inform all partners of the agreement to implement a therapy review.

Both signed protocols also indicated that one signatory was the practice manager, and she had signed as such. She signed the same section of the protocol as the complainant's partner, confirming her authority to approve the therapy review protocol. Again, it was not for ProStrakan or its agents to determine whether a signatory was or was not the practice manager.

ProStrakan took no part in the implementation of the therapy review service. Section 1 of the protocol clearly indicated that a named agency would undertake the therapy review. Section 4.2 of the protocol specified that 'ProStrakan will have no role in the service provision beyond reimbursement of [the agency]'.

ProStrakan was not given a list of patients by the practice. Rather, this was given to the agency pharmacist who conducted the agreed therapy review. ProStrakan did not see, nor did it wish to see, any patient details pertaining to the therapy review service. Nor did ProStrakan have any direct contact with any patient involved in the therapy review. According to Section 4.10 of the signed protocol agreement, 'Each patient will be informed of any change to their medication and any additional instructions necessary to ensure appropriate use, in accordance with the wishes of the individual practice'.

The complainant had indicated that the practice had provided a list of patients so that they could be written to. In writing to these patients, the pharmacist had therefore complied with the wishes of the practice as per the agreed protocol.

The preference for Adcal-D_3 on page 3 of the protocol was completed by the complainant's partner. He had also signed Section 5 of the protocol, to confirm that he had seen and reviewed the patient lists generated as a result of the therapy review and authorised the therapy review pharmacist to implement the agreed changes. In writing to the specified patients with letters indicating Adcal-D_3, ProStrakan's agent had again complied with the documented wishes of the practice and in accordance with the protocol agreement. These letters were discussed with, and approved by, the complainant's partner prior to being sent to patients.

A table listed the requested documentation and detailed the ProStrakan response in each case. ProStrakan provided copies of signed protocols dated 6 May 2008 and 21 July 2008. The company explained that no additional training materials were provided to the site. Full details of the service were contained in the protocol document and discussed with the site prior to implementation. Letters to patients contained patient identifiers and were therefore not seen or kept by ProStrakan.

ProStrakan regretted that the implementation of the therapy review service had led to a complaint at this site. Nevertheless, ProStrakan and its agents had acted at all times in agreement with the protocol which was signed by persons at the site who identified themselves as individuals with the authority to sign such a document. ProStrakan noted that there appeared to be a degree of misunderstanding on the part of the complainant as to the roles of ProStrakan and the agency pharmacist. It also appeared that the protocol

signatories did not abide by their commitment to inform all partners of the agreement, despite there being ample opportunity between the first and second visits of the therapy review staff for this to occur. ProStrakan trusted that its response clarified the situation and allayed the complainant's concerns.

In response to a request for further information ProStrakan explained that the first practice authorisation form was still valid for a visit on 21 July. However, due to the delay between the first and second visits, as a matter of good working practice, a second form was used. This was to ensure that the information pertaining to the practice and its instructions for the pharmacist were accurate and up-to-date.

The complainant's signature was not sought on 21 July. The complainant's partner had identified himself as lead GP with authorisation to sign the practice authorisation form on behalf of the practice. Both 6 May and the 21 July forms identified him as a lead GP for the practice. On both occasions, he signed in the box marked 'Lead GP Signature'. The sentence immediately prior to his signature read 'We are duly authorised to sign this form on behalf of the practice'. Since he had identified himself twice as a lead GP with the authority to allow the therapy review on behalf of the practice, there was no indication to the pharmacist that further signatures were required prior to commencement of the review. Had the practice indicated that the complainant's signature was necessary prior to commencement of the review, it would have been sought and the review would not have proceeded until it had been obtained.

Instructions about the status of the authorising GP were given to the representatives and agency personnel in the respective briefing documents.

For representatives, the brief stated, 'The pharmacist will only carry out work on behalf of the GP as authorised by a signature on the authorisation form… Only if authorised by the signatory GP in section 5 of the authorisation form will the pharmacist conduct any medication changes on the practice computer system for each patient'. The brief contained instructions to discuss the protocol 'in detail' (but not during a sales call) and to seek the agreement of the individual and ensure that any objections had been dealt with. Section 1 of the protocol, the practice authorisation form, contained boxes for recording of lead GP details and also for the lead GP signature. Identification of lead GP(s) and their approval was therefore covered during the detailed discussion of the protocol. Once all discussions had taken place, the brief stated the authorisation form might be completed and 'must be signed by an authorised practice signatory'.

The agency brief stated 'The [agency] pharmacist will attend the practice to:

- Clarify aims and objectives of the service
- Ensure Practice understanding of the service'

Furthermore, on the day of the visit, 'The pharmacist will check the Authorisation Form to ensure that all relevant sections are completed and signed as appropriate'. The [agency] pharmacist would therefore check that the authorisation form had been signed by a lead GP or would obtain their signature if it was not already on the form.

The agency pharmacists were instructed to check the authorisation form on the day of their visit and to clarify the aims and objectives of the service and ensure practice understanding of the service. These discussions allowed the practice staff to highlight any issues that might impact upon the implementation of the service.

ProStrakan understood that a full discussion between the pharmacist and practice staff occurred on 21 July, as evidenced by the completion and signature of a new protocol on that date. This was in accordance with the brief given to the agency pharmacists.

On 21 July the practice staff raised no concerns or issues regarding the authorisation of the therapy review, or any others that might have impacted on the implementation of the review.

The steps taken to ensure the lead GP had agreement from all other partners in the practice were as follows: the representative was briefed to discuss the protocol, including the practice authorisation form, in detail; the representative was briefed to 'Ask the GP to seek agreement from all the partners in the practice. An agreed time period for this is crucial and will also test the individual's commitment to the offer. If necessary re-book another appointment, to gain confirmation from other partners that they are happy with the service'. It should be noted that the practice did not request an additional appointment for other partners, during either the visit on 6 May or 21 July; the pharmacist was briefed to check the authorisation form and ensure practice understanding of the service; in discussing and checking the authorisation form, the representative and pharmacist highlighted to practice staff the requirement for signature by individuals authorised to do so on behalf of the practice and the individual who identified himself as lead GP was required to sign the practice authorisation form which [on the form dated 6 May] stated 'We hereby authorise [the agency] to undertake the Calcium and Vitamin D Supplementation Project and will inform all partners of this agreement' [the authorisation form dated 21 July described the service as 'the calcium and vitamin D_3 Deficiency Clinical Review']. The complainant's partner duly signed this section on both 6 May and 21 July and therefore gave this undertaking twice.

In summary, both the representative and pharmacist were briefed to ensure that practice staff fully understood the protocol and its requirements. Such an understanding was based on a comprehensive discussion of each of the individual parts of the protocol, including the practice authorisation form. This form allowed the practice to identify staff with

the requisite authority to approve the therapy review. The form also required that the signatories commit to informing all partners of the agreement.

In this case, discussions with the practice staff occurred twice and on neither occasion did practice staff raise issues or concerns regarding either the signatories' authority or the awareness of other partners at the practice of the therapy review. Had any concerns been raised regarding these issues, the therapy review would not have occurred unless and until the issues had been resolved.

PANEL RULING

The Panel noted that the complainant firstly queried whether appropriate signatories had been obtained for the practice authorisation form. That dated 6 May 2008 jointly listed the complainant and his partner as the lead GP and the second signatory as the practice manager. The declaration on the practice authorisation form read 'We hereby authorise [the agency] to undertake the Calcium and Vitamin D supplementation project and will inform all partners of this agreement. We are duly authorised to sign on behalf of the practice', beneath which the complainant's partner alone signed as the lead GP and the second signatory was the practice manager. The form subsequently signed on 21 July did not mention the complainant; his partner alone was listed as lead GP and signed as such alongside the practice manager.

The Panel noted that the Calcium and Vitamin D Supplementation Clinical Review Protocol required the practice authorisation form to be completed and signed by an authorised independent prescriber and the practice manager prior to any work being undertaken. The Panel noted ProStrakan's explanation that representatives were instructed to discuss the protocol in detail during a non-promotional call and ensure that any objections had been dealt with. Identification of lead GPs and their approval was dealt with during the detailed discussion of the protocol. In addition ProStrakan explained that the pharmacist was instructed to check the authorisation form to ensure that all relevant sections were complete and signed by a lead GP and to ensure practice understanding of the service. According to ProStrakan on neither 6 May or 21 July did practice staff raise issues or concerns regarding either the signatories' authority or the awareness of other partners and the practice of the service.

The Panel noted that the complainant, the senior GP partner, was concerned that the service had been completed without his authorisation. The Panel noted ProStrakan's submission that neither the company nor its agents were responsible for determining whether a medical professional who signed as a lead GP was indeed the lead GP or verifying that signatories had abided by their commitment to inform all partners of the agreement to implement a therapy review. The Panel considered, however, that there might be circumstances where further enquiries about such matters ought to be made. The Panel queried whether the representative and pharmacist should have sought the complainant's view given the reference to him on the first form. The Panel noted however that he had not signed the declaration on the first form. The declaration placed the responsibility on the signatories to inform '... all partners of this agreement'.

ProStrakan had submitted that on 21 July the practice staff raised no concerns or issues regarding the authorisation of the therapy review. The Panel considered that whilst it was impossible to determine exactly what had transpired at the practice there was insufficient evidence before it to indicate that the service had not been authorised as required by the protocol. The Panel considered that although it might have been prudent to obtain the complainant's signature the failure to do so, given the declaration signed by his partner, did not mean that high standards had not been maintained. Thus the Panel ruled no breach of Clause 9.1.

The Panel noted that the service was run by an agency on behalf of ProStrakan. A pharmacist ran the service at the practice in consultation with the lead GP. Section 4.2 of the protocol provided that ProStrakan played no role in the service provision other than reimbursement of the service provider. ProStrakan did not receive a list of practices or any patient details or have any patient contact. The pharmacist wrote to patients in accordance with the agreed protocol. There was no evidence before the Panel that ProStrakan had received patient data and/or written to patients as alleged. No breach of Clause 9.1 was ruled in this regard.

The Panel noted the complainant's allegation that whoever did the survey also wrote [Adcal-D_3] which was promoted and made by ProStrakan. The Panel noted that any change in medicine as a result of the service had to be agreed by the lead doctor. The Panel considered that it did not have an allegation about whether the service was acceptable, as the complainant had made no specific comment in this regard. The Panel noted that pharmaceutical companies could provide medical and educational goods and services, including therapy review programmes. Such services needed to comply with the Code, particularly Clause 18.4. It was not necessarily a breach of the Code for products from the company providing the service to be prescribed. Taking all the circumstances into account the Panel decided in relation to the complainant's allegation that there was no breach of Clause 18.1 and ruled accordingly.

Given its rulings above the Panel also ruled no breach of Clause 2.

Complaint received	**4 December 2008**
Case completed	**12 February 2009**

ANONYMOUS HEALTH PROFESSIONALS v ASTRAZENECA

Conduct of representative

Two complaints were received from anonymous, non-contactable, hospital health professionals about the conduct of the same AstraZeneca representative.

One health professional complained that the representative had recently discussed the unpublished Jupiter (Justification for the Use of Statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin) data. The representative admitted to the complainant that she 'should not strictly be discussing the data yet' but she had clearly initiated the discussion and facilitated further questioning regarding the data.

During the conversation it became apparent that her line manager knew that she was discussing the data despite the fact that to do so was a clear breach of the Code.

An anonymous consultant also complained that discussions were initiated by the representative regarding the unpublished Jupiter data.

The detailed response from AstraZeneca is given below.

The Panel examined the representatives' briefing material. The results of the study would be of interest to health professionals. The first briefing, a voicemail, was very positive and stated that 'This is great news for Crestor' and this would give customers the outcome data that many had been waiting for before positioning Crestor positively in their guidelines. It would give confidence for customers to use and recommend Crestor more widely. The voicemail concluded with a question 'What actions should I take?'. The answer made it clear that the study was completed in a group of patients who were outside the UK licence and 'so you must not proactively raise this study with customers. It is against the AstraZeneca Code of Conduct and the ABPI Code of Practice to promote any study that is outside of a product licence'.

All the briefing material was very clear that Crestor did not have a marketing authorization for reducing cardiovascular (CV) events or saving lives and therefore could not and must not be so promoted. Further guidance was given that sales calls must not be engineered to encourage customers to ask for further information on the use of Crestor to reduce CV events. The company had prepared a reactive statement for representatives to respond to unsolicited enquiries. Representatives had been instructed not to proactively raise the study with customers.

The representative's line manager had reissued the briefings by email with a reminder. The email also praised the account team and named two individuals (not the representative in these cases) for the high number of referrals they had generated '… through [the regional medical affairs executive] post Jupiter'. This was the highest in the UK. In the Panel's view this comment could be evidence that representatives were being encouraged to engineer discussions about the data and thus generate requests to be referred elsewhere for a response.

The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. The Panel had some concerns about the material supplied to representatives but also noted the company's submission that the representative's line manager witnessed her responding correctly to a request for information about Jupiter on two occasions. The Panel considered that the allegation was a serious one but it did not consider that evidence had been provided by either complainant to show that on the balance of probabilities the representative in question had promoted an unlicensed indication as alleged and no breach was ruled.

Two separate complaints were received from anonymous non-contactable, hospital health professionals about the conduct of the same AstraZeneca UK Limited representative.

Case AUTH/2190/12/08

COMPLAINT

An anonymous health professional complained that named AstraZeneca representative had recently discussed the unpublished Jupiter (Justification for the Use of Statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin) data. The representative admitted to the complainant that she 'should not strictly be discussing the data yet' but she clearly initiated the discussion and facilitated further questioning regarding the data.

During the conversation it became apparent that her line manager knew that she was discussing the data despite the fact that to do so was a clear breach of the Code.

After careful consideration the complainant considered that there was no alternative but to report the matter.

Case AUTH/2194/12/08

COMPLAINT

An anonymous consultant complained that during recent meetings the same representative had initiated discussions about the unpublished Jupiter data.

This was alleged to be a breach of the Code.

* * * * *

When writing to AstraZeneca the Authority asked it to respond in relation to Clauses 3.2 and 15.2 of the Code.

Cases AUTH/2190/12/08 and AUTH/2194/12/08

RESPONSE

AstraZeneca noted that both allegations were in essence identical and that the source of the allegations appeared to be very similar. Whilst it was always difficult to verify the independence and authenticity of anonymous complainants, AstraZeneca believed the spirit of the Code required it to deal with the complaints in good faith.

AstraZeneca took the complainants' allegations very seriously and recognised the need for proper and thorough investigations. Regrettably, there was very little detail in either complaint, such as dates, which would have assisted in dealing with them. The first letter was from a 'health professional' in a specific hospital which allowed AstraZeneca to check the activity of the representative in this hospital. The second was simply from a 'consultant' in a same region of England.

The Jupiter study was presented at the American Heart Association congress and simultaneously published online in the New England Journal of Medicine on 9 November 2008. Jupiter was a placebo-controlled cardiovascular outcomes study using rosuvastatin (Crestor) in a primary prevention population, which was a group of patients not included in the currently licensed indications for Crestor. The unprecedented reductions in mortality and morbidity, which had resulted in the study being prematurely terminated in March 2008, suggested that the Jupiter study publication would achieve a very high level of media attention. AstraZeneca was thus particularly concerned to ensure that all employees were fully briefed on the requirements of the Code and that no one had any doubt about what they could and could not say about the study. Accordingly, a series of cascaded briefings took place using teleconferences and webex technology, emails, voicemails and face-to-face briefings for all relevant employees immediately after the online publication on Sunday, 9 November. Copies of these briefings were provided. Details of the briefings relevant to the named representative were given.

All briefings were signed off by two signatories as required by the Code. The briefings, *inter alia*, stated that the Jupiter study publication could not be raised proactively with any health professional and gave a brief, factual reactive statement which could be used by representatives if the study was mentioned by one of their customers. The representative confirmed that she had received all relevant briefings. The reactive statement was as below:

> 'The Jupiter study was recently presented at the AHA and published in the New England Journal of Medicine. The Jupiter study showed that those subjects who received Crestor had a reduction in cardiovascular events vs placebo. As this study is in a population that is out of licence I cannot discuss the results – if you would like more information on the Jupiter study I can arrange a visit from one of the AZ Regional Medical Affairs team or request information be sent to you by Medical Information'.

Case AUTH/2190/12/08

AstraZeneca submitted that it was not against the Code to discuss unpublished material, although 'data on file' needed to be made available on request without delay and any unpublished data referred to in promotional material needed to be within the existing licensed indications for the medicine. Due to the results being potentially price sensitive, they were embargoed until the publication date. Therefore the representative did not know the results before Monday, 10 November (she was unaware that they had been published online at 2pm the previous day in the New England Journal of Medicine) and therefore no results could possibly have been discussed prior to that time. Therefore AstraZeneca had looked at all calls in the hospital in question until the date of the complaint letter. Eight different health professionals were seen in 10 separate calls between 10 November and 8 December. The representative received comprehensive briefings throughout this time period and was fully aware of her obligations in dealing with the Jupiter data. The representative had no recollection of any conversations taking place in any of the visits where the Jupiter study results were discussed, apart from using the agreed reactive statement in response to a question.

On two separate occasions the line manager had accompanied the representative when asked about Jupiter and on both occasions she responded correctly, using the short factual statement and offering referral to a regional medical affairs executive or medical information if the customer wanted more details.

The business manager, the line manager and the Head of medical affairs for primary care had all spent time discussing the allegations with the representative and had given her every opportunity to admit to 'a genuine mistake', if this had indeed occurred. Sufficient time had also been allowed during the investigation for the representative to recall anything that did not come to mind at initial interviews. The representative and all three separate individuals were consistent in their belief that no inappropriate discussions had taken place.

The representative's line manager and the business manager were questioned about the allegations. Both denied any knowledge of the alleged discussions taking place. The line manager had in fact issued two additional briefing emails on 13 and 26 November to her team, reusing the signed-off briefing materials, and stressing the importance of adopting the correct approach to any queries around Jupiter. As elsewhere in AstraZeneca, the investigation concluded that there was a strong focus on governance and compliance issues in this region and all briefings stressed the importance of complying with the Code.

Case AUTH/2194/12/08

AstraZeneca submitted that the points made above in response to Case AUTH/2190/12/08 were relevant to this case. The representative was again contacted to discuss the second complaint and asked to try to recall any situation where a discussion about Jupiter might have taken place that could have been misinterpreted by the consultant as off-label promotion. The representative was consistent and adamant that no such discussions had taken place.

Conclusion

AstraZeneca took allegations about representative conduct extremely seriously and there would be serious repercussions for a representative who proactively discussed information about a medicine which was inconsistent with its marketing authorization.

AstraZeneca was confident that the various briefing materials that were issued both centrally and locally were timely, comprehensive and clear. The representative was of exemplary character and performance and the statements had been consistent and robust throughout the investigations. In addition, the evidence of the line manager (including as a witness to two calls on health professionals) and the business manager had also been consistent and robust in support of the representative. AstraZeneca could find no evidence to support the allegations and therefore it denied breaching Clauses 3.2 and 15.2 in respect of either complaint.

FURTHER INFORMATION

In response to a request for further information, AstraZeneca confirmed that its representatives were not given a copy of Jupiter nor were they instructed how to access the paper online. The paper was never distributed to the sales teams in any other format and they were not instructed as how to use it. The briefing material that representatives received, referred to above, contained clear instructions. AstraZeneca referred again to the precise wording to use in response to enquiries about Jupiter from health professionals and how these requests must be referred to AstraZeneca's medical team or medical information.

To refer these enquiries the representatives had to generate a referral in the AstraZeneca database. This was then passed on to the appropriate regional medical affairs executive.

In the line manager's email of 26 November 2008, the manager used content and language consistent with the clear instruction above and also internal jargon with reference to 'the high number of referrals they have generated through [the regional medical affairs executive] post Jupiter'. It would be expected that a high number would be generated given the extensive media coverage of the study's results in both the lay and medical press but only if the representatives followed the clear instruction above and generated the appropriate referral. The manager confirmed this was the case in her subsequent sentence in the email when she referred to this number providing 'clear evidence that we are communicating with our customers through the right channels'. Clearly the line manager's intention in this email was to reinforce the instruction on Jupiter communication and congratulate the team on appearing to diligently follow that instruction.

The reference to 'code breaches' in this email to the team referred to the fact that cases published by the PMCPA in the Code of Practice Review relevant to the sales team were discussed as part of their governance framework and such cases had been recently discussed at the manager's local meeting.

This email was supplied to the PMCPA in good faith in response to the original complaints as relevant evidence in support of appropriate action taken by company representatives and their manager in response to Jupiter. AstraZeneca appreciated however that when this email was considered in isolation by an individual not familiar with AstraZeneca process and internal jargon, it could potentially be misunderstood. However, AstraZeneca hoped that its explanation had addressed any concerns that the Panel might originally have had.

PANEL RULING

The Panel noted that the complainants were anonymous and non-contactable. When an allegation had been made about what a representative had said to a health professional it was difficult to determine precisely what had occurred. The parties' accounts often differed. In

similar cases, before the Panel made its ruling, the company's response had been sent to the complainant for comment. This was not possible here.

The Panel noted that both complainants referred to a discussion about unpublished data. It was not necessarily a breach of the Code to discuss unpublished data. It would be a breach of the Code to promote an unlicensed medicine or indication irrespective of whether data was published.

The Panel examined the briefing material provided by AstraZeneca. It considered that given the results of the study there would be interest from health professionals. The first briefing to all the CV salesforce was a voicemail dated 10 November. The Panel noted that the voicemail was very positive stating that 'This is great news for Crestor' and this would give customers the outcome data that many had been waiting for before positioning Crestor positively in their guidelines. It would give confidence for customers to use and recommend Crestor more widely. The voicemail concluded with a question 'What actions should I take?'. The answer made it clear that the study was completed in a group of patients who were outside the UK licence and 'so you must not proactively raise this study with customers. It is against the AstraZeneca Code of Conduct and the ABPI Code of Practice to promote any study that is outside of a product licence'.

All of the briefing material was very clear that Crestor did not have a marketing authorization for reducing CV events or saving lives and therefore could not and must not be so promoted. Further guidance was given that sales calls must not be engineered to encourage customers to ask for further information on the use of Crestor to reduce CV events. The company had prepared a reactive statement for representatives to respond to unsolicited enquiries. Representatives had been instructed not to proactively raise the study with customers. The line manager had reissued the briefings with a reminder. The Panel was concerned about the reference in an email dated 26 November to '… several code breaches across the UK'. The email also praised the account team and named two individuals (not the representative in these cases) for the high number of referrals they had generated '… through [the regional medical affairs executive] post JUPITER'. This was the highest in the UK. In the Panel's view this comment could be evidence that representatives were being encouraged to engineer discussions about the data and thus generate requests to be referred elsewhere for a response.

The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. The Panel had some concerns about the material supplied to representatives but noted the company's submission that the representative's line manager witnessed her responding correctly to a request for information about Jupiter on two occasions. The Panel considered that the allegation was a serious one but it did not consider that evidence had been provided by either complainant to show that on the balance of probabilities the representative in question had promoted an unlicensed indication as alleged and no breach of Clauses 3.2 and 15.2 was ruled in both cases.

Complaints received	**AUTH/2190/12/08**	**10 December 2008**
	AUTH/2194/12/08	**17 December 2008**
Cases completed		**20 January 2009**

CASE AUTH/2191/12/08

NOVARTIS v ROCHE

Bondronat detail aid

Novartis complained about a Bondronat (ibandronic acid) hospital detail aid produced by Roche. Novartis marketed Zometa (zoledronic acid). Both Zometa and Bondronat were bisphosphonates which could be used to prevent skeletal events in patients with breast cancer and bone metastases.

The detailed response from Roche is given below.

Novatis alleged that the claim 'Innovative, multi-targeted bone protection' which appeared as an integral part of the product logo was misleading and incapable of substantiation. Health professionals would believe that Bondronat had a mechanism of action or benefit not previously seen with regard to bone protection.

In the Panel's view most readers would assume that innovative was a description of the multi-targeted bone protection and that somehow Bondronat was a different approach to therapy which was not so. The Panel considered the claim ambiguous, misleading and incapable of substantiation as alleged. Breaches of the Code were ruled.

The claim appeared on the front page and on many other pages of the detail aid and would be read in light of the data on the relevant page. The Panel considered that on the front cover, which featured the phrase 'Time for a change?' the claim would be seen as comparative ie it would encourage doctors to change from their current therapy choice to one which offered innovative, multi-targeted bone protection. The Panel considered that such a comparison was misleading. A breach of the Code was ruled.

Page 8 of the detail aid, headed 'Time to compare tolerability', compared oral Bondronat with iv zoledronic acid. Beneath the claim 'Oral Bondronat has a better tolerability profile than zoledronic acid' a bar chart, adapted from Body *et al* (2005), compared the percentage of patients with adverse events throughout the study (Bondronat 65%, zoledronic acid 76%) and with pyrexia and flu-like symptoms during the first 3 days (Bondronat 1%, zoledronic acid 27%). No p values were given.

Novartis stated that a reasonable comparison could not be made between iv and oral formulations given over different time lines without any statistical statement. This point in itself was misleading. In addition it was not stated that zoledronic acid had been administered intravenously; it was not immediately clear from the graph that an oral preparation was being compared with an iv preparation.

The detail aid promoted iv Brondronat and oral Bondronat; such a comparison was alleged to be unbalanced in the absence of data on the iv formulation of Bondronat. Since this adverse drug reaction (ADR) was also seen with iv Bondronat a similar statement could quite fairly be made for iv Bondronat. Novartis therefore contended that to suggest this statement was a product specific ADR was disingenuous and clearly disparaged zoledronic acid.

Novartis alleged that use of Body *et al* (2005) demonstrated cherry picking data, not allowing fair and balanced review of the data which was also borne out by Roche's view that the juggling skeleton on the front page of the detail aid suggested that patients might be able to change between the two formulations of Bondronat, where clinically relevant. But this data did not allow for the choice between the two Roche formulations.

In Novartis' view, a lack of comparative data for iv Bondronat [to oral ibandronate or comparing iv Bondronat to iv zoledronic acid] should preclude the use of this study in the detail aid.

The Panel noted Roche's submission that oral Bondronat and iv zoledronic acid were the two most frequently prescribed bisphosphonates in UK hospitals for the treatment of bone disease in metastatic breast cancer. The detail aid was for use in hospitals. Both companies agreed that most clinicians knew that zoledronic acid was given iv. Two bullet points beneath the bar chart clearly stated the infusion rate of zoledronic acid and thus made its iv presentation clear although these were much less prominent than the preceding bar chart and heading which made no mention of zoledronic acid's presentation. Nonetheless on balance the Panel did not consider the page misleading or disparaging because it failed to make the iv presentation of zoledronic acid sufficiently clear as alleged. Given the intended audience, readers would know that zoledronic acid was administered intravenously. No breaches of the Code were ruled. The Panel did not consider that the page suggested that adverse reactions were product specific or that in that regard zoledronic acid had been disparaged. Nor did the Panel consider it misleading to fail to mention comparable data for iv Bondronat as alleged. Further, the Panel did not consider that the use of Body *et al* (2005) represented unfair cherry picking as alleged. No breach of the Code was ruled.

The claim 'No evidence for any treatment-related deterioration in renal function was seen for any patient – as assessed by change from baseline in

[serum creatinine], calculated [creatinine clearance rate] or in the urinary excretion of markers of glomerular and tubular function' outlined the results and conclusions of von Moos *et al* (2006), a comparison of the renal safety of iv Bondronat 6mg infused over 15 (n=101) or 60 minutes (n=26). A graph on page 10 showed changes in calculated creatine clearance rate over time for both treatment groups. 'Time not to exclude patients due to renal dysfunction' was the heading on page 11 which set out the dosage and administration of iv Bondronat including that for patients with moderate or severe renal impairment.

Novartis explained that it raised both points (the claim and the heading cited above) simultaneously because individually and together they gave an unbalanced and misleading view of Bondronat's safety profile in terms of renal toxicity, and therefore did not support rational prescribing. Breaches of the Code were alleged.

The Panel noted that Novartis had not provided any reasons to support its allegation that the two claims at issue were in breach of the Code.

The Panel noted that pages 9 and 10 of the detail aid were tagged 'Safety' and together gave details of a study by von Moos *et al* which evaluated the renal safety of Bondronat 6mg infused over 15 or 60 minutes every 3-4 weeks for 6 months. The study concluded that a 15 minute infusion was well tolerated with a safety profile consistent with that of the 60 minute infusion. The study authors noted, however, that in the 15 minute group 3% of patients (n=3) had an increase in serum creatine levels over the limit established by the primary endpoint. In one of these patients Bondronat was listed as one of three possible causes and serum creatinine returned to normal levels after the study end. The Panel noted that section 4.8, Undesirable Effects of the iv Bondronat summary of product characteristics (SPC) detailed the adverse reactions from a phase III study with Bondronat 6mg (n=152); an increase in creatinine occurred more often in Bondronat patients (2%) than in placebo treated patients (0.6%). Renal and urinary disorders were listed as uncommon. The oral Bondronat SPC listed renal and urinary disorders as uncommon.

The Panel noted that on page 10 two bullet points referred to the 3 patients in the 15 minute group who had a serum creatinine increase over the primary endpoint limit. These details preceded and were of equal prominence to the bullet point detailing the study conclusions including the claim at issue 'No evidence for any treatment-related deterioration in renal function was seen for any patient – as assessed by change from baseline in [serum creatinine], calculated [creatinine clearance] or in the urinary excretion of markers of glomerular and tubular function'. The Panel considered that the claim was misleading; the authors had cited Bondronat as a possible cause for increased serum creatinine in one patient. A breach of the Code was ruled. The Panel did not consider that the claim failed to encourage rational prescribing. No breach of the Code was ruled.

The claim 'Time not to exclude patients due to renal dysfunction' headed page 11 of the detail aid which was tagged 'IV Dosing'. The Panel noted that the page reproduced the iv Bondronat dosing regimen for patients with varying degrees of renal function and showed that even patients with severe renal impairment could be treated with Bondronat albeit at a reduced dose with an infusion time of 1 hour. Thus impaired renal function was not a contraindication to Bondronat. The Panel thus did not consider the claim was either misleading or that it did not encourage rational prescribing. No breach of the Code was ruled.

Page 13 headed 'Time to review bisphosphonates in hospital' discussed a clinical audit (Barrett-Lee *et al* 2006) which captured data on the whole patient experience of receiving iv bisphosphonate therapy. A diagram depicted the total mean patient time spent on a hospital unit for iv pamidronate as 2 hours 36 minutes and iv zoledronic acid 1 hour 38 minutes. A pie chart overleaf on page 14 showed the reasons for attending hospital for breast cancer patients receiving iv bisphosphonates; 77% of them attended a hospital unit for that therapy alone whereas 23% at the same time also received chemotherapy and/or a clinic appointment.

Novartis stated that there was no explanation of how these findings related to either Bondronat formulation. In the absence of data for either formulation this lack of comparison alone was misleading and disparaging as it seemed only to question whether patients should be switched from pamidronate or zoledronic acid as highlighted by the use of the phrase 'Time to review bisphosphonates in hospitals'.

Furthermore, the conclusions on page 14 did not reflect the aim of the study to 'provide insight into the intravenous administration of bisphosphonates and how this impacts on hospital resources and patient experiences'. Novartis alleged that the conclusions 'IV bisphosphonate administration involved time, cost and inconvenience for patients' and 'IV bisphosphonate administration involved substantial resource use for clinics and staff' were all-embracing as there was no data for iv Bondronat.

Novartis stated that iv Bondronat would sit somewhere between iv zoledronic acid and iv pamidronate in terms of overall time, cost and inconvenience for patients, and that for hospitals these would therefore be equally applicable arguments for substantial resource use for iv Bondronat for clinics and staff. Therefore by explicitly highlighting these requirements only for competitor products Roche had unfairly disparaged zoledronic acid and pamidronate.

The Panel noted that the audit was designed to quantify the current time involved in the

administration of iv bisphosphonates and how this might impact on patient experience and cancer unit capacity. The Panel considered that the objective of the audit was clear. The audit was not designed to detect differences between specific bisphosphonates; however page 13 stated that the audit findings were that on average iv pamidronate patients spent 2 hours 36 minutes on a hospital unit and iv zoledronic acid patients spent 1 hour 38 minutes. The Panel considered that in the detail aid in question, and in the absence of a statement to the contrary, these times would be taken as an implied comparison with Bondronat. Barrett-Lee *et al*, however, had noted these times only in order to show that the preparation of bisphosphonates infusion was not the main driver for the time that patients spent on a unit and once the infusion was started they were, on average, completed in a similar time to the manufacturers' recommendations of 90 minutes for pamidronate and 15 minutes for zoledronic acid. This was not made clear in the detail aid. The Panel considered that some readers might assume that the infusion time for zoledronic acid was 1 hour 38 minutes which was not so. Similarly the recommended infusion time for pamidronate was 90 minutes and not the 2 hours and 36 minutes referred to in the detail aid. The Panel noted Barrett-Lee's view that it appeared use of an iv bisphosphonate with a shorter infusion time might not release as much capacity for a day care unit as might be expected. The Panel noted the emphasis throughout the detail aid of a 15 minute infusion time for Bondronat. It considered that without any information as to how long patients might spend on a unit in addition to the time receiving Bondronat iv and/or to not give the recommended infusion times for zoledronic acid and pamidronate created a misleading impression and exaggerated the differences between the products which could not be substantiated and was disparaging. Breaches of the Code were ruled.

The Panel noted that page 14 only referred to the iv administration of bisphosphonates and the time, cost and inconvenience for patients and the staff and clinic resources needed. In that regard the Panel did not consider that the lack of data for Bondronat meant that the claims were all embracing as alleged. No breach of the Code was ruled.

'Time to consider resources' headed page 15 which detailed the UK interim analysis of a pharmacoeconomic study (Wardley *et al* 2004). A bar chart compared the average resource time burden per patient of several aspects involved in the administration of iv zoledronic acid and oral Bondronat; preparation of the infusion, infusion duration, and time spent by the clinician, nurse, laboratory technician and pharmacist. Oral Bondronat was described as a cost-effective choice compared with zoledronic acid. 'Time to save resources' headed page 16 which compared the additional clinician and nurse time required with zoledronic acid iv administration vs oral Bondronat over 12 months.

Novartis alleged that there was no substantiation that this pharmacoeconomic study (n=9) reflected the average resource and time burden; no reasonable conclusions could realistically be drawn from the very small population. Its use in promotional material was an unfair, scientifically invalid comparison and misleading. Novartis alleged that these findings were all-embracing and would be equally applicable to iv Bondronat which was not represented.

The Panel noted that Wardley *et al* was an interim analysis of the UK data from an open label sub-study of a clinical trial which assessed medical care utilization of iv zoledronic acid (4mg infusion every four weeks (n=5)) and oral Bondronat (50mg daily (n=4)).

The Panel did not consider that data from such a small interim analysis, for which no statistical analysis was reported, was sufficiently robust to support the claims made from it. The Panel was particularly concerned about the claim 'Bondronat – a cost effective choice'. The Panel queried the validity of extrapolating clinician and nursing minutes saved per patient per infusion from a data set of 5 to the saving of 16 hours/patient/year to 200 days per 100 patients per year. The Panel considered the material on pages 15 and 16 were misleading as alleged. Breaches of the Code were ruled.

Page 17 headed 'Time for flexibility and consistency of care' summarised the data in the detail aid in a series of bullet points. Novartis stated that Roche was unable to give specific assurances on points highlighted above which included unfair comparisons between the products.

The Panel noted Novartis alleged that unfair comparisons between the products were covered by the rulings above. No specific clauses of the Code had been cited in relation to this page but Novartis had referred to matters highlighted above. The Panel noted that one comparative claim was featured 'Time for a cost-effective approach to resources. 16 hours time saved per patient per year with oral Bondronat vs zoledronic acid'. The Panel considered that this claim was covered by its ruling above. Breaches of the Code were ruled.

Finally, Novartis alleged that Roche's use of the American Society of Clinical Oncology (ASCO) guidelines to support the claims 'Time to initiate …' and 'Time to maintain …' was misleading as Bondronat was not licensed in the US for the prevention of skeletal related events in patients with breast cancer and bone metastases and therefore had not been reviewed within the guidelines.

The Panel noted that the heading 'Time to initiate with IV Bondronat 15 minute infusion (for the majority of patients)' introduced the bullet point

'ASCO Guidelines 2003 – Bisphosphonates should be given to women with lytic destruction on X-ray and receiving systemic treatment for [metastatic bone cancer]'. The heading 'Time to maintain treatment with oral Bondronat' introduced the bullet point 'ASCO Guidelines 2003 – Bisphosphonates should continue until decline in patients performance status'.

The Panel noted that the ASCO Guideline 2003 did not include data from ongoing phase III studies of oral and iv Bondronat as they had not been fully published. The two bullet points in question, however, were included on a page which summarised the whole of the Bondronat detail aid and in that context readers would assume the ASCO Guidelines reviewed Bondronat data and that was not so. The bullet points were misleading and incapable of substantiation as alleged. Breaches of the Code were ruled.

Novartis Pharmaceuticals UK Ltd complained about a Bondronat (ibandronic acid) hospital detail aid (P116402) produced by Roche Products Limited. The date of preparation for the detail aid was March 2007 and so the 2006 Code applied. However the clauses cited by Novartis (7.2, 7.3, 7.4, 7.8, 7.10 and 8.1) were the same in the 2006 Code as in the 2008 Code. The case was therefore considered under the 2008 Code.

Roche explained that although the detail aid was withdrawn in mid 2008 many of the claims it contained had been used in subsequent materials.

Inter-company dialogue had not been successful. Novartis marketed Zometa (zoledronic acid). Both Zometa and Bondronat were bisphosphonates which could be used to prevent skeletal events in patients with breast cancer and bone metastases.

Bisphosphonates were available in both intravenous (iv) and oral formulations. Overall in UK hospitals in 2007 3% of patients with metastatic bone disease due to breast cancer received oral clodronate, 15% iv pamidronate, 23% oral Bondronat and 59% iv zoledronic acid. In addition, oral clodronate and oral Bondronat were also prescribed in primary care for metastatic bone disease, following initial prescriptions in secondary care. Thus oral Bondronate and iv zoledronic acid were the agents with the greatest UK hospital usage in the treatment of metastatic bone disease in breast cancer in 2007. Intravenous Bondronat and iv clodronate were only used in 2% and less than 1% respectively, of breast cancer patients treated with iv bisphosphonates in 2007.

The detail aid was entitled 'Time for a change?' The front page featured a red banner 'Now with 15 minute infusion' and a visual of a skeleton juggling what appeared to be an infusion pack, a clock and a pill blister pack of tablets. The detail aid discussed various features of oral and iv Bondronat including mechanism of action, efficacy, tolerability, safety, iv dosing and clinical audit.

1 Claim 'Innovative, multi-targeted bone protection'

This claim appeared as an integral part of the product logo on the front page and on several other pages throughout the detail aid.

COMPLAINT

Novartis alleged that the claim was misleading and incapable of substantiation in breach of Clauses 7.2, 7.3 and 7.4 of the Code. Health professionals would believe that Bondronat had a mechanism of action or benefit not previously seen with regard to bone protection.

Roche had contended in inter-company dialogue that 'innovative' referred to the fact that Bondronat was the only amino-bisphosphonate available in both oral and iv formulation which thus offered health professionals the flexibility to treat patients with the same molecule in the formulation most suited to their particular circumstances.
Novartis contended that:

- Roche did not explain its interpretation of innovation within the detail aid to allow the health professional to form a judgement on whether they agreed that this was a credible claim.
- Novartis believed that suggesting the presentation was an innovative feature for an amino-bisphosphonate gave it undue emphasis, and the compound would be perceived as having greater superiority whereas 'innovative' was meaningless in terms of clinical significance, or mechanism of action. The non-nitrogen containing bisphosphonate, clodrondate had long been available as an oral and iv preparation. In this clinical setting nitrogen containing bisphosphonates had the same mechanism of action regardless of formulation.
- 'Multi-targeted bone protection' could not be considered innovative because in the prevention of skeletal events nitrogen containing bisphosphonates all had the same mechanism of action (Roelofs *et al* 2006).
- Novartis believed Roche had confused innovation with flexibility of use. Novartis was confident that a health professional would recognise this statement as a claim for flexibility rather than innovation, but in the absence of all the facts this was misleading.

RESPONSE

Roche stated that the claim 'Innovative, multi-targeted bone protection' referred to several proven features of Bondronat. 'Multi-targeted' referred to its mode of action which, in common with other amino-bisphosphonates, had a number of mechanisms which might be responsible for the prevention of skeletal events in metastatic bone disease. 'Bone protection' referred to the prevention

of skeletal related events by Bondronat therapy.

'Innovative' referred to the availability of Bondronat not only as an iv preparation, but also as an effective oral preparation for the treatment of metastatic bone disease. The amino-bisphosphonates, eg pamidronate, zoledronic acid and Bondronat, had a different mode of action from earlier non nitrogen-containing bisphosphonates such as clodronate and this had led to greater efficacy in the prevention of skeletal related events and pain in metastatic bone disease. However, as a consequence of this novel mode of action, the amino-bisphosphonates might also induce gastrointestinal side effects (Suri *et al* 2001) which could limit patient acceptability and thus efficacy of oral formulations. For example, oral pamidronate had greater efficacy against skeletal morbidity at 600mg/day than at 300mg/day, but patients could not tolerate the 600mg/day dose due to gastrointestinal side effects (Diener 1996). As a result, oral pamidronate was not marketed. Bondronat was the only amino-bisphosphonate which could be given orally in a sufficiently large dose to be highly effective against the skeletal complications of malignancy, while having gastrointestinal tolerability sufficient to allow patients to comply with daily oral dosing (Bondronat oral summary of product characteristics (SPC), Diel 2004).

Thus 'innovative' referred to the fact that Bondronat was the only amino-bisphosphonate available as an oral formulation for the treatment of metastatic bone disease which allowed patients a choice in how and where their bisphosphonate care was delivered, added to which the availability of both oral and iv formulations allowed health professionals to treat patients with the same molecule in the formulation most suited to their particular circumstances.

Thus all elements of the claim 'Innovative, multi-targeted bone protection' were capable of substantiation, were not misleading and were not in breach of Clauses 7.2, 7.3, and 7.4.

PANEL RULING

The Panel did not consider that many readers would interpret the claim 'Innovative, multi-targeted bone protection' as submitted by Roche. In the Panel's view most readers would assume that innovative was a description of the multi-targeted bone protection and that somehow Bondronat was a different approach to therapy which was not so. The Panel considered the claim ambiguous, misleading and incapable of substantiation as alleged. Breaches of Clauses 7.2 and 7.4 were ruled.

The claim appeared on the front page and on many other pages of the detail aid and would be read in light of the data on the relevant page. The Panel considered that on the front cover, which featured the phrase 'Time for a change?' the claim would be seen as comparative ie it would encourage doctors to change from their current therapy choice to one which offered innovative, multi-targeted bone protection. Similarly on other pages of the detail aid where Bondronat was compared with other bisphosphonates a comparison would be implied. The Panel considered that such a comparison was misleading. A breach of Clause 7.3 was ruled.

2 Comparison of oral Bondronat with iv zoledronic acid

Page 8 of the detail aid, headed 'Time to compare tolerability', compared oral Bondronat with iv zoledronic acid in metastatic breast cancer. Beneath the claim 'Oral Bondronat has a better tolerability profile than zoledronic acid' a bar chart, adapted from Body *et al* (2005), compared the percentage of patients with adverse events throughout the study (Bondronat 65%, zoledronic acid 76%) and with pyrexia and flu-like symptoms during the first 3 days (Bondronat 1%, zoledronic acid 27%). No p values were given.

COMPLAINT

Novartis stated that a reasonable comparison could not be made between iv and oral formulations given over different time lines without any statistical statement and in itself was misleading.

Novartis also noted that it was not stated that zoledronic acid had been administered intravenously and so it was not immediately clear that an oral preparation was being compared with an iv preparation. The page did not state very clearly that it was not a comparison of like with like, but of an oral vs an iv bisphosphonate. Furthermore, it would not be immediately obvious from the graph that two different formulations were being compared. Whilst most clinicians would know that zoledronic acid was administered as an iv infusion this sentence and accompanying graph were the most prominent on the page and both were incomplete.

The detail aid promoted iv Brondronat and oral Bondronat; such a comparison was alleged to be unbalanced in the absence of data on the iv formulation of Bondronat. Since this adverse drug reaction (ADR) was also seen with iv Bondronat a similar statement could quite fairly be made for iv Bondronat (ie oral Bondronat had a better tolerability profile than iv ibandronic acid). Novartis therefore contended that to suggest this statement was a product specific ADR in promotional material was disingenuous and clearly disparaged 4mg zoledronic acid.

Novartis alleged that use of Body *et al* (2005) demonstrated cherry picking data, not allowing fair and balanced review of the data was also borne out by Roche's inter-company correspondence wherein it stated that the juggling skeleton on the front page

of the detail aid suggested that patients might be able to change between the two formulations of Bondronat, where clinically relevant. But this data did not allow for the choice between the two Roche formulations.

Roche maintained that '… consistency of care' (used as a strapline on page 17) related to the potential to maintain treatment on the same compound but different formulations. The ability to use the same compound in its various presentations was Roche's defence for the 'Innovation' strapline. Novartis alleged, in the light of these facts, that to not include iv Bondronat was unbalanced, misleading and disparaging.

Roche's contention was that this was a study which compared these two formulations at the time and it had presented the comparison as reported. However, in Novartis' view, a lack of comparative data for iv ibandronate [to oral ibandronate or comparing iv Bondronat to iv zoledronic acid] should preclude the use of this study in this promotional material.

Roche's offer to amend the claim 'Oral Bondronat has a better tolerability profile than zoledronic acid' did not meet all of Novartis' concerns. Novartis strongly believed that the use of this study as well as the strapline was in breach of Clauses 7.2, 7.3, 7.8 and 8.1.

RESPONSE

Roche stated that with regards to the data from a comparative study of oral Bondronat and iv zoledronic acid, this was a comparison of medicines for the same intended purpose as required by Clause 7.3, which showed material, relevant, substantiable and representative features of those medicines. The two bisphosphonates most frequently prescribed in UK hospitals for the treatment of bone disease in metastatic breast cancer were oral Bondronat and iv zoledronic acid. It was therefore relevant to UK clinical practice to compare these two agents. Tolerability data was an important element in the prescribing decision/choice for any medicine. This study gave clinicians a view of the most common adverse effects that their patients might experience with each medicine. The large study was conducted as a multi-centre randomised trial, which added weight to its findings. The graph on page 8 was relevant to the comparison being made and had been faithfully reproduced, as in the original publication. Thus the graph provided an accurate, clear, fair, balanced view, substantiated by the cited reference, and thus was not misleading or disparaging.

The iv status of zoledronic acid had not been omitted from the page even though Novartis agreed that most clinicians knew that zoledronic acid was given iv. The page stated that zoledronic acid was given iv as 4mg infused over 15 minutes every 4 weeks. This statement was shown in larger type than that used on the graph and was placed below the graph so that readers could not miss it. The page in question did not state or imply that pyrexia and flu-like symptoms were a product specific ADR of zoledronic acid.

As shown above, iv Bondronat was only prescribed to 2% of UK breast cancer patients given iv bisphosphonate in 2007. To include this medicine in a comparison of the two most commonly used bisphosphonate therapies for this disease would therefore give it an undue and unsuitable prominence and it would provide an incorrect comparator for the study shown on page 8. However, data for the tolerability of both iv Bondronat vs placebo and oral Bondronat vs placebo were shown on the two preceding pages of the detail aid. This allowed any clinician who wished to learn of the tolerability of iv Bondronat to be readily informed by the sales representative. Roche had been very careful not to include any comparison between the iv Bondronat and zoledronic acid data, as it was not valid to make such cross-study comparisons.

Roche rejected Novartis' concerns that page 8 was disingenuous, misleading, or disparaging to 4mg zoledronic acid and it was not in breach of Clauses 7.2, 7.3, 7.8, and 8.1, nor was it incapable of substantiation.

PANEL RULING

The Panel noted Roche's submission that oral Bondronat and iv zoledronic acid were the two most frequently prescribed bisphosphonates in UK hospitals for the treatment of bone disease in metastatic breast cancer. The detail aid was for use in hospitals. Both companies agreed that most clinicians knew that zoledronic acid was given iv. Two bullet points beneath the bar chart clearly stated the infusion rate of zoledronic acid and thus made its iv presentation clear although these were much less prominent than the preceding bar chart and heading which made no mention of zoledronic acid's presentation. Nonetheless on balance the Panel did not consider the page misleading or disparaging because it failed to make the iv presentation of zoledronic acid sufficiently clear as alleged. Given the intended audience, readers would know that zoledronic acid was administered intravenously. No breach of Clauses 7.2, 7.4, 7.8 and 8.1 was ruled. The Panel did not consider that the page suggested that adverse reactions were product specific or that in that regard zoledronic acid had been disparaged. No breach of Clause 8.1 was ruled. Nor did the Panel consider it misleading to fail to mention comparable data for iv Bondronat as alleged. No breach of Clauses 7.2, 7.3, 7.8 and 8.1 was ruled on this point. Further, the Panel did not consider that the use of Body *et al* (2005) represented unfair cherry picking as alleged. No breach of Clause 7.2 was ruled.

During its consideration of this case the Panel noted

that the claim 'Oral Bondronat has a better tolerability profile than zoledronic acid' was a strong unequivocal claim which contained no reference to time. It preceded a bar chart adapted from Body *et al* (2005) which was a 12 week study comparing the safety profiles of Bondronat and iv zoledronic acid (n=254). The chart showed that in the first 3 days of the study 1% and 27% of patients had pyrexia and flu-like symptoms in the Bondronat and zoledronic acid groups respectively. The authors stated that these symptoms were probably or possibly treatment related. Throughout the trial (overall) the percentage of patients reporting adverse events was 65% in the Bondronat group and 76% in the zoledronic acid group. No p value was given for either the 3 day or the overall comparison and so there was no way of knowing if the results, which favoured Bondronat, represented a statistically significant difference between the products. The Panel was concerned that the data presented was insufficient to support the claim and asked that both parties be advised of its concerns.

3 Claims 'No evidence for any treatment-related deterioration in renal function …' (page 10) and 'Time not to exclude patients due to renal dysfunction' (page 11)

The claim 'No evidence for any treatment-related deterioration in renal function was seen for any patient – as assessed by change from baseline in [serum creatinine], calculated [creatinine clearance rate] or in the urinary excretion of markers of glomerular and tubular function' was a bullet point on page 10 which outlined the results and conclusions of von Moos *et al* (2006) which was a comparison of the renal safety of iv Bondronat 6mg infused over 15 (n=101) or 60 minutes (n=26). A graph showed changes in calculated creatine clearance rate over time for both treatment groups.

'Time not to exclude patients due to renal dysfunction' was the heading on page 11 which set out the dosage and administration of iv Bondronat including that for patients with moderate or severe renal impairment.

COMPLAINT

Novartis explained that both of these points were raised simultaneously because individually and together they gave an unbalanced and misleading view of Bondronat's safety profile in terms of renal toxicity, and therefore did not support rational prescribing. Breaches of Clauses 7.2 and 7.10 were alleged.

RESPONSE

Roche submitted that renal safety was a particular issue in metastatic patients treated with bisphosphonates, Roche therefore presented data to address this issue. However, the two points cited by Novartis described different aspects of the data for Bondronat.

In the past, rapid infusion of bisphosphonates led to renal damage. The claim 'No evidence for treatment-related deterioration in renal dysfunction' appeared on a page designed to reassure clinicians that a 15 minute iv infusion of Bondronat had shown adequate renal safety in this setting. The claim was a conclusion from a clinical trial specifically designed to investigate renal safety in 102 breast cancer patients with bone metastases receiving iv Bondronat infused over 15 minutes every 3-4 weeks for 6 months. This was accepted by the European Medicines Evaluation Agency (EMEA) as evidence of renal safety in the registration filing for the 15 minute infusion. The claim on page 10 clearly showed that renal function was assessed by four, well accepted, parameters. However, in order not to mislead the reader, Roche had also referred to the three patients who had an increase in serum creatinine above primary endpoint in the study. The investigators assigned those to non-permanent or treatment unrelated changes, as shown in the reference. Roche noted that section 4.4 of the SPC for Bondronat stated that 'Clinical studies have not shown any evidence of deterioration in renal function with long term Bondronat therapy'.

The claim 'Time not to exclude patients due to renal dysfunction' headed page 11 which showed the iv Bondronat dosing schedule for different levels of renal impairment. As shown, the rate of infusion and the dose must be modified with declining renal function, but it was possible to use Bondronat in patients with impaired renal function. Roche believed that such data should appear prominently in the detail aid and should not be restricted to the prescribing information, to encourage responsible prescribing of Bondronat.

The claims at issue neither individually nor in combination gave an unbalanced and misleading view of Bondronat's safety profile in terms of renal toxicity. Furthermore, both efficacy and safety data for iv Bondronat were reported in the detail aid thereby presenting the risk/benefit profile of the medicine to enable health professionals to form their own opinion of the therapeutic value of Bondronat. Roche denied breaches of Clauses 7.2 and 7.10.

PANEL RULING

The Panel noted that Novartis had alleged that the two claims at issue 'No evidence for any treatment-related deterioration was seen for any patient…' and 'Time not to exclude patients due to renal dysfunction' individually and together gave an unbalanced and misleading view of Bondronat's safety profile in terms of renal toxicity, and therefore did not support rational prescribing. No reasons for this allegation were given.

The Panel noted that pages 9 and 10 of the detail

aid were tagged 'Safety' and together gave details of a study by von Moos *et al* which evaluated the renal safety of Bondronat 6mg infused over 15 or 60 minutes every 3-4 weeks for 6 months. The study concluded that a 15 minute infusion was well tolerated with a safety profile consistent with that of the 60 minute infusion. The study authors noted, however, that in the 15 minute group 3% of patients (n=3) had an increase in serum creatine levels over the limit established by the primary endpoint (an increase in serum creatinine from baseline of ≥ 44.2_mol/L at any point in the study). In one of these patients Bondronat was listed as one of three possible causes and serum creatinine returned to normal levels after the study end. The Panel noted that section 4.8, Undesirable Effects of the iv Bondronat SPC detailed the adverse reactions from a phase III study with Bondronat 6mg (n=152); an increase in creatinine occurred more often in Bondronat patients (2%) than in placebo treated patients (0.6%). Renal and urinary disorders were listed as uncommon. The oral Bondronat SPC listed renal and urinary disorders as uncommon.

The Panel noted that on page 10 two bullet points referred to the 3 patients in the 15 minute group who had a serum creatinine increase over the primary endpoint limit. These details preceded and were of equal prominence to the bullet point detailing the study conclusions including the claim at issue 'No evidence for any treatment-related deterioration in renal function was seen for any patient – as assessed by change from baseline in [serum creatinine], calculated [creatinine clearance] or in the urinary excretion of markers of glomerular and tubular function'. The Panel considered that the claim was misleading; the authors had cited Bondronat as a possible cause for increased serum creatinine in one patient. A breach of Clause 7.2 was ruled. The Panel did not consider that the claim failed to encourage rational prescribing. No breach of Clause 7.10 was ruled.

The claim 'Time not to exclude patients due to renal dysfunction' headed page 11 of the detail aid which was tagged 'IV Dosing'. The Panel noted that the page reproduced the iv Bondronat dosing regimen for patients with varying degrees of renal function and showed that even patients with severe renal impairment could be treated with Bondronat albeit at a reduced dose with an infusion time of 1 hour. Thus impaired renal function was not a contraindication to Bondronat. The Panel thus did not consider the claim was either misleading or that it did not encourage rational prescribing. No breach of Clauses 7.2 and 7.10 was ruled.

During its consideration of this point the Panel noted that von Moos *et al* only recruited patients with an adequate renal function – creatinine clearance of ≥50ml/min. Page 9 gave details of the study population and endpoints but did not state the entry criteria. The Panel noted that pages 9 and 10 of the detail aid referred to the 15 minute infusion time and cited von Moos *et al* in support. The Panel noted that a 15 minute infusion time was not licensed for use in patients with a creatinine clearance of <50ml/min. Pages 9 and 10 failed to include the entry criteria for von Moos *et al* or make it clear that the study conclusions regarding the renal safety profile of the 15 minute infusion only related to those with a creatinine clearance ≥50ml/min. The Panel requested that the parties be advised of its view in this regard.

4 Statement 'Time to review bisphosphonates in hospital' (page 13 – page 14)

Page 13 headed 'Time to review bisphosphonates in hospital' discussed a clinical audit (Barrett-Lee *et al* 2006) which captured data on the whole patient experience of receiving iv bisphosphonate therapy. A diagram depicted the total mean patient time spent on a hospital unit for iv pamidronate as 2 hours 36 minutes and iv zoledronic acid 1 hour 38 minutes. A pie chart overleaf on page 14 showed the reasons for attending hospital for breast cancer patients receiving iv bisphosphonates; 77% of them attended a hospital unit for that therapy alone whereas 23% at the same time also received chemotherapy and/or a clinic appointment.

COMPLAINT

Novartis stated that there was no explanation of how these findings related to either Bondronat formulation. In the absence of data for either formulation this lack of comparison alone was misleading and disparaging as it seemed to serve no purpose other than to question whether patients should be switched from pamidronate or zoledronic acid as highlighted by the use of the phrase 'Time to review bisphosphonates in hospitals'.

Furthermore, the conclusions made on page 14 did not reflect the aim of the study to 'provide insight into the intravenous administration of bisphosphonates and how this impacts on hospital resources and patient experiences'. Novartis alleged that the conclusions on page 14, 'IV bisphosphonate administration involved time, cost and inconvenience for patients' and 'IV bisphosphonate administration involved substantial resource use for clinics and staff' were all-embracing as there was no data for iv Bondronat.

The fact that according to the SPC for iv Bondronat, infusion times ranged from 15 – 60 minutes depending on patients' renal function also meant that had it been included in the study, results for this compound might well lie between 1 hour 38 minutes seen for zoledronic acid and 2 hours 36 minutes seen for pamidronate. This was opposed to the 15 minute infusion time in the SPC for zoledronic acid and 90-270 minute infusion time in the SPC for pamidronate. In fact, iv Bondronat would sit somewhere between iv zoledronic acid and iv pamidronate in terms of overall time, cost and inconvenience for patients, and that for hospitals these would therefore be

equally applicable arguments for substantial resource use for iv ibandronate for clinics and staff. Therefore by explicitly highlighting these requirements only for competitor products Roche had unfairly disparaged zoledronic acid and pamidronate.

Novartis therefore alleged that the use of Barrett-Lee *et al* breached Clauses 7.2, 7.3, 7.10 and 8.1 for iv zoledronic acid and Clauses 7.2, 7.3 and 8.1 for iv pamidronate.

RESPONSE

Roche reiterated that breast cancer patients survived on average 2.5 years after diagnosis of metastatic bone disease and might receive bisphosphonates for much of that time, but they might not always receive concurrent chemotherapy. The iv administration of bisphosphonates, as shown on page 13, required patients to spend between 1.5 and 2.5 hours on the chemotherapy units of 3 major oncology hospitals in the UK. The chart on page 14 showed that for more than three quarters of visits to these hospitals, patients attended solely to receive an iv bisphosphonate.

These data were collected in order to inform NHS resource planning in the 3 centres. As chemotherapy unit capacity was very limited in some UK centres, such data helped health professionals to assess whether that capacity was being used to best effect. They might also assist the provision of greater choice to patients in how their therapy was delivered.

In this audit, no data were reported for iv Bondronat due to the clinicians' preference to prescribe pamidronate or zoledronic acid as their iv bisphosphonate of choice. This reflected the very low level of iv Bondronat prescribed in UK hospitals (2% of total iv usage). Introduction of iv Bondronat into this audit would have given it undue prominence for its UK market share. Oral Bondronat was also not included in the audit as the aim was to measure iv bisphosphonate usage. The audit was designed to examine the experience of patients receiving iv bisphosphonates as a group of agents, rather than the choice of iv bisphosphonate. Therefore, the use of this study was not misleading or disparaging but rather reflected NHS interest in resource and cost saving as well as maximising patient experience.

Page 14 which represented the conclusions from the study referred to iv bisphosphonates as a group and did not mention any specific product. This and the fact that the outcomes of the audit, in terms of the iv bisphosphonates used, reflected the prescribing habits of the clinicians involved in the study, as well as the wider prescribing community nationally, meant that the use of this study was not in breach of Clauses 7.2, 7.3, 7.10 and 8.1 for iv zoledronic acid nor was it in breach of Clauses 7.2, 7.3, and 8.1 for pamidronic acid.

PANEL RULING

The Panel noted that the audit was designed to quantify the current time involved in the administration of iv bisphosphonates and how this might impact on patient experience and cancer unit capacity. The Panel considered that page 13 made the objective of the audit clear. The audit was not designed to detect differences between specific bisphosphonates however page 13 stated that the audit findings were, that on average iv pamidronate patients spent 2 hours 36 minutes on a hospital unit and iv zoledronic acid patients spent 1 hour 38 minutes. The Panel considered that in the detail aid in question, and in the absence of a statement to the contrary, these times would be taken as an implied comparison with Bondronat. Barrett-Lee *et al*, however, had noted these times only in order to show that the preparation of bisphosphonates infusion was not the main driver for the time that patients spent on a unit and once the infusion was started they were, on average, completed in a similar time to the manufacturers' recommendations of 90 minutes for pamidronate and 15 minutes for zoledronic acid. This was not made clear in the detail aid. The Panel considered that some readers might assume that the infusion time for zoledronic acid was 1 hour 38 minutes which was not so. Similarly the recommended infusion time for pamidronate was 90 minutes and not the 2 hours and 36 minutes referred to in the detail aid. The Panel noted Barrett-Lee *et al's* view that it appeared use of an iv bisphosphonate with a shorter infusion time might not release as much capacity for a day care unit as might be expected. The Panel noted the emphasis throughout the detail aid of a 15 minute infusion time for Bondronat. It considered that without any information as to how long patients might spend on a unit in addition to the time receiving Bondronat iv and/or to not give the recommended infusion times for zoledronic acid and pamidronate created a misleading impression and exaggerated the differences between the products which could not be substantiated and was disparaging. Breaches of Clauses 7.2, 7.3, 7.10 and 8.1 were ruled.

The Panel noted that page 14 only referred to the iv administration of bisphosphonates and the time, cost and inconvenience for patients and the staff and clinic resources needed. In that regard the Panel did not consider that the lack of data for Bondronat meant that the claims were all embracing as alleged. No breach of Clause 7.10 was ruled.

5 Time to consider resources (page 15) and Time to save resources (page 16)

'Time to consider resources' headed page 15 which detailed the UK interim analysis of a pharmacoeconomic study (Wardley *et al* 2004). A bar chart compared the average resource time burden per patient of several aspects involved in the administration of iv zoledronic acid and oral

Bondronat; preparation of the infusion, infusion duration, and time spent by the clinician, nurse, laboratory technician and pharmacist. Oral Bondronat was described as a cost-effective choice compared with zoledronic acid.

'Time to save resources' headed page 16 which compared the additional clinician and nurse time required with zoledronic acid iv administration vs oral Bondronat over 12 months.

COMPLAINT

Novartis alleged that there was no substantiation that this pharmacoeconomic study (n=9) reflected the average resource and time burden; no reasonable conclusions could realistically be drawn from the very small population. As it was such a small population use of this study in promotional material was an unfair, scientifically invalid comparison and misleading. This was additionally misleading due to the presence of a later publication on pharmacoeconomics (Botteman *et al* 2006) which considered all available bisphosphonates, and their cost per quality adjusted life year (QUALY).

Novartis alleged that these findings were misleading, all-embracing and would be equally applicable to iv Bondronat. This compound though was not represented.

Novartis therefore alleged that the use of Wardley *et al* was in breach of Clauses 7.2, 7.3 and 7.8.

RESPONSE

Roche submitted that the pharmacoeconomic study on page 15 showed a comparison of hospital resources required to administer the two leading bisphosphonates in the UK for the treatment of bone metastasis in breast cancer. The low use of iv Bondronat in the UK reflected the fact that it was not used in the hospitals conducting this study and it was irrelevant to this comparison of leading agents. To introduce iv Bondronat, for comparative purposes might well have led to confusing data, as the health professionals involved were not accustomed to this agent in their routine practice.

There were only a small number of repeated observations in the study, as was customary for such pharmacoeconomic analyses. The variation in timing of repetitive processes such as preparation and dispensing was carefully monitored and more observations were added if there was great variability. In this study, the variation between repeat timings did not require additional measurements.

The results of this study were further supported by De Cock *et al* 2005 which was also referenced on page 15. However, Botteman *et al* was not relevant to this page, as it provided no actual measurements of time and resource usage for either oral or iv Bondronat administration. For iv Bondronat these data were estimated as an average of values for pamidronate and zoledronic acid and the 15 minute Bondronat infusion time was omitted.

The graph on page 16 (time to save resources) extrapolated the data from the study on page 15, to demonstrate how the differences in resources required to administer the two medicines might add up for different numbers of patients in a unit.

Roche believed that this study shown on pages 15 and 16 was not an invalid comparison nor was it misleading and its use was not in breach of Clauses 7.2, 7.3, and 7.8.

PANEL RULING

The Panel noted that Wardley *et al* was an interim analysis of the UK data from an open label sub-study of a clinical trial which assessed medical care utilization of iv zoledronic acid (4mg infusion every four weeks (n=5)) and oral Bondronat (50mg daily (n=4)).

The Panel did not consider that data from such a small interim analysis, for which no statistical analysis was reported, was sufficiently robust to support the claims made from it on pages 15 and 16. In that regard the Panel was particularly concerned about the claim 'Bondronat – a cost effective choice'. The Panel queried the validity of extrapolating clinician and nursing minutes saved per patient per infusion from a data set of 5 to the saving of 16 hours/patient/year to 200 days per 100 patients per year. The Panel considered the material on pages 15 and 16 were misleading as alleged. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled.

6 Summary page 17 – Time for flexibility and consistency of care

In a series of bullet points page 17 summarised the data presented in the detail aid.

COMPLAINT

Novartis stated that Roche had agreed to change the heading to page 17 together with other non-specified changes. Roche was unable to give specific assurances. The points requiring reassurance included unfair comparisons between the products as highlighted above.

RESPONSE

Roche had agreed, to change the statement 'Time for flexibility and consistency of care' on this page and in order not breach that agreement, it would ensure that the statement was changed not only in letter but in spirit. However, Roche did not believe

that the Code required it to inform Novartis of the exact wording of the new headline. The remaining statements on the page repeated points from previous pages which, as shown above, Roche did not believe were in breach of the Code. Comparisons of medicines for the same needs or intended purposes were permitted if relevant, substantiable and representative features were compared and Roche believed this applied to the comparisons in the detail aid.

PANEL RULING

The Panel noted Novartis alleged that unfair comparisons between the products were covered by the rulings above. No specific clauses of the Code had been cited in relation to this page but Novartis had referred to matters highlighted above. The Panel noted that one comparative claim was featured on page 17 for oral Bondronat and zoledronic acid, 'Time for a cost-effective approach to resources. 16 hours time saved per patient per year with oral Bondronat vs zoledronic acid'. The Panel considered that this claim was covered by its ruling at point 5 above. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled.

7 Use of American Society of Clinical Oncology (ASCO) Guidelines on page 17

COMPLAINT

Finally, Novartis wanted to highlight its concerns about use of ASCO guidelines to support the claims 'Time to initiate …' and 'Time to maintain …'.

The reasons were that Bondronat was not licensed in the US for the prevention of skeletal related events in patients with breast cancer and bone metastases and therefore ibandronate had not been reviewed within the guidelines. Novartis submitted that UK health professionals would not immediately be aware of this and therefore alleged that use of the ASCO guidelines to support these claims was misleading to UK health professionals in breach of Clauses 7.2 and 7.3.

RESPONSE

Roche stated that page 17 clearly stated that the ASCO guidelines on bisphosphonates were from 2003. ASCO summarised the data then available and noted that data from ongoing phase III studies of oral and iv Bondronat were presented at ASCO 2003, but were not included in the guideline report because they had not been fully published. The publication also stated that the choice of bisphosphonates was broader outside the US and each country must make its own relative cost benefit assessment.

These points from the 2003 ASCO publication, plus the fact that pivotal data for Bondronat efficacy were published in 2004 to 2006 (Body 2004; Body *et al* 2004 and Diel) made it unreasonable to suggest that, because the ASCO guideline did not include Bondronat, the principles of administration of bisphosphonates for metastatic disease should not apply to Bondronat.

In the absence of detailed UK guidelines on bisphosphonate therapy in metastatic bone disease, Roche quoted the latest (2003) ASCO guidelines. However, on page 17 of the detail aid there was no attempt to claim that the ASCO guidelines recommended Bondronat as a therapy. The guidelines were very clearly cited to demonstrate what ASCO considered to be best practice in the administration of bisphosphonates, as a class, for metastatic bone disease – that they be given to women with certain X-ray findings and continued until decline in performance status. These statements were neither misleading, nor in breach of Clauses 7.2, 7.3 or 7.4.

PANEL RULING

The Panel noted that the heading 'Time to initiate with IV Bondronat 15 minute infusion (for the majority of patients)' introduced the bullet point 'ASCO Guidelines 2003 – Bisphosphonates should be given to women with lytic destruction on X-ray and receiving systemic treatment for [metastatic bone cancer]'. The heading 'Time to maintain treatment with oral Bondronat' introduced the bullet point 'ASCO Guidelines 2003 – Bisphosphonates should continue until decline in patients performance status'.

The Panel noted that the ASCO Guideline 2003 did not include data from ongoing phase III studies of oral and iv Bondronat as they had not been fully published. The Panel did not accept, as suggested by Roche, that page 17 of the detail aid made no attempt to claim the ASCO Guideline recommended Bondronat as a therapy. The two bullet points in question were included on a page which summarised the whole of the Bondronat detail aid and in that context readers would assume the ASCO Guidelines reviewed Bondronat data and that was not so. The bullet points were misleading and incapable of substantiation as alleged. Breaches of Clauses 7.2 and 7.3 were ruled.

Complaint received **12 December 2008**

Case completed **4 March 2009**

CASE AUTH/2192/12/08

VOLUNTARY ADMISSION BY PFIZER

Lipitor Journal advertisement

Pfizer voluntarily admitted that it had breached the undertaking and assurance which it had given in Case AUTH/2093/1/08 in that the Lipitor fireman journal advertisement, found in breach of the Code in May 2008, had been published in the November 2008 edition of Practitioner.

The detailed response from Pfizer is given below.

The Authority's Constitution and Procedure provided that the Director should treat an admission as a complaint if it related to a potentially serious breach of the Code or if the company failed to take appropriate action to address the matter. A breach of undertaking was a serious matter and the admission was accordingly treated as a complaint.

The Panel noted that the undertaking in Case AUTH/2093/1/08 was signed on 15 May 2008. The advertisement had re-appeared in the Practitioner, November 2008. The Panel ruled a breach of the Code which was not appealed by Pfizer.

The Panel noted a 'Withdrawal of Advertisement' form sent from Pfizer to its agents referred to the 'Lipitor Fireman advert' with a reference number LIP 2933. The form stated 'Please destroy all copies of the advertisements above. Original artwork may be kept but must be stored electronically with sufficient safeguards to ensure that it cannot be used accidentally. We suggest creating a folder called "Withdrawn materials: not to be used".' Recipients were to sign the form and return it to the Lipitor brand manager to confirm that they had complied with the notice. The form stated that the advertisements must not be used again.

The Panel was concerned that the form did not state why the advertisement had to be withdrawn. In the Panel's view the knowledge that an advertisement was in breach of the Code would have emphasised the urgency of complying with the withdrawal request. The form only listed one advertisement (ref LIP 2933) and did not alert the reader that there might be a number of executions of the same advertisement. The reader had no way of knowing how many advertisements had to be destroyed.

Further, the agencies were asked to destroy the advertisements but advised that they might keep the original artwork. The way such artwork was kept was left up to the agency with a suggestion that it create a folder called 'Withdrawn materials: not to be used' and that there be sufficient safeguards to prevent accidental use.

Finally the form required the recipient to confirm that they had complied with the notice. In the Panel's view the recipients should have been required to confirm that they had destroyed the advertisements, giving details of each reference number, and to give details as to their arrangements for storing the original artwork.

The Panel considered that if pharmaceutical companies were to allow agencies to store original artwork that was not to be used then they must ensure, and take responsibility for, the agencies creating a secure archive for such material. To merely suggest on a form the creation of a folder called 'Withdrawn materials: not to be used' was unacceptable.

The Panel noted that a letter from Pfizer's healthcare media company stated that '… [Pfizer's media buyer] instructed [Pfizer's healthcare media company] not to run the 'Fireman' advertisement due to an out of date product [prescribing information]. Whilst this was forwarded to our production department, there has been a breakdown in communication'. The Panel noted that out of date prescribing information was not at issue in Case AUTH/2093/1/08.

Overall the Panel did not consider that Pfizer had a sufficiently robust procedure for ensuring that material ruled in breach of the Code was not re-used. Agencies were not told why advertisements had to be withdrawn or given precise enough instructions about how many advertisements had to be withdrawn; they were allowed to make their own arrangements for secure storage of original artwork. On balance the Panel considered that high standards had not been maintained. A breach of the Code was ruled which was appealed by Pfizer.

Upon appeal the Appeal Board noted that Pfizer's 'Withdrawal of Advertisement' form stated clearly at the top that 'The following advertisements must be removed from any media in which they appear immediately. These advertisements must not be used again. The items affected are: …'. This was followed by a description of the advertisement (Lipitor fireman advertisement) a reference number, LIP 2933 and the section listing the name of the journals where it appear referred to all press as indicated in an attached document or similar. The form then stated 'Please destroy all copies of the advertisements above. Original artwork may be kept but must be stored electronically with sufficient safeguards to ensure that it cannot be used accidentally. We suggest creating a folder called "withdrawn materials: not to be used"'. The form stated that it must be signed by the recipient to confirm that they had complied with the notice and that the advertisements in the journals

mentioned should not appear after 8 May 2008. The forms were signed and returned by the recipients.

The Appeal Board considered that the form made it clear that copies of the advertisement at issue were to be destroyed and not used again.

The Appeal Board noted that Pfizer's media buyer had confirmed with Pfizer's healthcare media company that it would not run the Lipitor fireman advertisement again. The replacement advertisement for Lipitor had subsequently been published 34 times in October and November although not in Practitioner. The first Lipitor advertisement to appear in the Practitioner since May 2008 was in November when Pfizer's healthcare media company incorrectly published the fireman advertisement.

The Appeal Board considered that it might have been helpful if Pfizer had stated on its form that the advertisement was being withdrawn because it was in breach of the Code. Correspondence from Pfizer's healthcare media company indicated that the advertisement had been withdrawn due to out-of-date prescribing information.

Nonetheless the Appeal Board considered that Pfizer had taken reasonable steps to endeavour to comply with its undertaking; it had been badly let down by its healthcare media company. The Appeal Board did not consider in the circumstances that Pfizer had failed to maintain high standards and it thus ruled no breach of the Code.

The Panel considered that Pfizer had endeavoured to comply with its undertaking. Although company procedures could have been more robust the company was also let down by one of its agents. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was a sign of particular censure and reserved for such. No breach of the Code was ruled.

Pfizer Limited voluntarily admitted that it had breached the undertaking and assurance which it had given in Case AUTH/2093/1/08 in that the Lipitor fireman journal advertisement, found in breach of Clauses 7.2 and 7.10 of the Code in May 2008, had been published again.

COMPLAINT

Pfizer explained that when notified of the outcome of Case AUTH/2093/1/08 it had followed internal processes to prevent the fireman advertisement being published again. This included asking all of the parties involved to confirm that they had destroyed all existing copies. Contrary to Pfizer's instruction, the advertisement had inadvertently appeared in the November 2008 edition of Practitioner.

Pfizer explained that in late April it was informed that the advertisement had been found in breach of the Code; Pfizer then telephoned its media buyer, to instruct it to notify its clients that the advertisement should be withdrawn – an email to this effect, which was sent from Pfizer's media buyer on 30 April was provided. In reply to this email Pfizer's healthcare media company stated that the fireman advertisement would not be used again.

Written confirmation of the ruling was received on 8 May after which Pfizer followed stringent communication procedures to ensure that the fireman advertisement was withdrawn from circulation and destroyed. Pfizer's notification emails to it's media buyer, its creative design agency, and its European brand team were provided, along with the signed responses from each of them, which stated that all copies of the advertisement would be destroyed and never used again.

On 26 September, although Pfizer's creative design agency emailed Pfizer's healthcare media company to run the new Lipitor 'fisherman' advertisement in the November edition of Practitioner, and attached the PDF of the advertisement to the email, the healthcare media company nonetheless published the withdrawn fireman advertisement.

Immediately upon hearing about this, Pfizer investigated the matter fully and discussed the seriousness of it with all parties involved. The publishers, Pfizer's healthcare media company, had assumed full responsibility for the error which was a result of a communication error within its own production department, and had assured Pfizer that measures had been taken to prevent this situation reoccurring.

* * * * *

The Authority's Constitution and Procedure provided that the Director should treat an admission as a complaint if it related to a potentially serious breach of the Code or if the company failed to take appropriate action to address the matter. A breach of undertaking was a serious matter and the admission was accordingly treated as a complaint. The Authority asked Pfizer to comment in relation to Clauses 2, 9.1 and 25.

* * * * *

RESPONSE

Pfizer stated in reply that there was no information or evidence to add to its initial admission. It strongly believed that its actions confirmed that it had absolutely maintained high standards, adhered to its undertaking and not brought the industry into disrepute and therefore was not in breach of Clauses 2, 9.1 or 25.

PANEL RULING

The Panel considered that an undertaking was an

important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that in Case AUTH/2093/1/08 the Lipitor fireman advertisement was ruled in breach of the Code. The Appeal Board considered that it exaggerated the urgency to prescribe which was incompatible with advice given to prescribers in the Lipitor summary of product characteristics (SPC). The undertaking was signed on 15 May 2008. The advertisement had re-appeared in the Practitioner, November 2008. The Panel ruled a breach of Clause 25.

The Panel noted a 'Withdrawal of Advertisement' form sent from Pfizer to its agents referred to the 'Lipitor Fireman advert' with a reference number LIP 2933. The form stated 'Please destroy all copies of the advertisements above. Original artwork may be kept but must be stored electronically with sufficient safeguards to ensure that it cannot be used accidentally. We suggest creating a folder called "Withdrawn materials: not to be used".' Recipients were to sign the form and return it to the Lipitor brand manager to confirm that they had complied with the notice. The form stated that the advertisements must not be used again. The Panel noted that the Pfizer European Brand Team who oversaw withdrawal of the advertisement from European Media with a UK circulation were provided with the form and an accompanying email which gave more details about the advertisement.

The Panel had a number of concerns about the form: The form did not state why the advertisement had to be withdrawn. In the Panel's view the knowledge that an advertisement was in breach of the Code would have emphasised the urgency of complying with the withdrawal request. The form only listed one advertisement (ref LIP 2933) and did not alert the reader that there might be a number of executions of the same advertisement (the advertisement at issue in Case AUTH/2093/1/08 had been ref LIP 2933e). The reader had no way of knowing how many advertisements had to be destroyed. In the Panel's view every reference code should have been listed.

Further, the agencies were asked to destroy the advertisements but advised that they might keep the original artwork. The Panel noted that the agency might own the original artwork. The way such artwork was kept was left up to the agency with a suggestion that it create a folder called 'Withdrawn materials: not to be used' and that there be sufficient safeguards to prevent accidental use.

Finally the form required the recipient to confirm that they had complied with the notice. In the Panel's view the recipients should have been required to confirm that they had destroyed the advertisements, giving details of each reference number, and to give details as to their arrangements for storing the original artwork.

The Panel considered that if pharmaceutical companies were to allow agencies to store original artwork that was not to be used then they must ensure, and take responsibility for, the agencies creating a secure archive for such material. To merely suggest on a form the creation of a folder called 'Withdrawn materials: not to be used' was unacceptable.

The Panel noted that a letter from Pfizer's healthcare media company stated that '…[Pfizer's Media Buyer] instructed [Pfizer's healthcare media company] not to run the 'Fireman' advertisement due to an out of date product [prescribing information]. Whilst this was forwarded to our production department, there has been a breakdown in communication'. The Panel noted that with regard to the matter at issue in Case AUTH/2093/1/08 out of date prescribing information was not a factor.

Overall the Panel did not consider that Pfizer had a sufficiently robust procedure for ensuring that material ruled in breach of the Code was not re-used. Agencies were not told why advertisements had to be withdrawn or given precise enough instructions about how many advertisements had to be withdrawn. Agencies were allowed to make their own arrangements for secure storage of original artwork. On balance the Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled which was appealed by Pfizer.

The Panel considered that Pfizer had endeavoured to comply with its undertaking. Although company procedures could have been more robust the company was also let down by one of its agents. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was a sign of particular censure and reserved for such. No breach of Clause 2 was ruled.

APPEAL BY PFIZER

Pfizer noted that the Panel had considered that there was not a sufficiently robust procedure for ensuring that material ruled in breach of the Code was not re-used. As previously described, Pfizer had followed stringent communication procedures to ensure that the fireman advertisement was withdrawn from circulation and destroyed. The publisher had not followed clear and explicit instructions to destroy the advertisement. In support of this, the publishers, Pfizer's healthcare media company, assumed full responsibility for the error, which was a result of a communication error within its production department.

The fireman advertisement was found in breach of Clauses 7.2 and 7.10 of the Code in May 2008 (Case AUTH/2093/1/08). Following that, emails of 12 May from the Lipitor brand manager to Pfizer's media buyer, Pfizer's creative design agency and the Pfizer european brand team, informed them of the

withdrawal of the advertisement. Each of these parties in return signed the 'Withdrawal of Advertisement' form which stated that all copies of the fireman advertisement must be destroyed and never used again. Following this, the advertisement was withdrawn from circulation and substituted with other advertisements.

Pfizer noted, in support of the robustness of its internal processes, the number of times the correct Lipitor advertisement (the fisherman) was published by other publishers in journals during the period of October to November 2008. This was confirmed by a media schedule and an email from Pfizer's media buyer (provided) which stated that the fisherman advertisement was published 34 times in October and November prior to the publication of the wrong advertisement (the fireman) by Pfizer's healthcare media company in November. The fact that the correct version of the advertisement had been published so many times previously made it difficult for Pfizer to anticipate this error; Pfizer felt very badly let down by its healthcare media company. This was especially so as it also had evidence that its creative design agency explicitly instructed Pfizer's healthcare media company via email to run the new Lipitor advertisement and attached the pdf of the correct fisherman advertisement to this email. The correct Lipitor advertisement was immediately distinguishable from the one found in breach of the Code as it featured a fisherman as opposed to a fireman.

Pfizer noted that the Panel had four main concerns about the 'Withdrawal of Advertisement' form.

i) The form did not state why the advertisement had to be withdrawn.

Whilst Pfizer agreed that the form could be improved upon to include a reason for withdrawal, it referred to a previous case, Case AUTH/2048/9/07 which bore many similarities to the current case. The case involved a voluntary admission from Grünenthal that it had breached the undertaking and assurance in relation to a journal advertisement for Versatis (lidocaine medicated plaster). A reason for withdrawal of the advertisement was not mentioned in the correspondence with the publishers. Despite this omission, the Panel did not rule a breach of Clause 9.1.

ii) The form only listed one advertisement (ref LIP 2933) and did not alert the reader that there might be a number of executions of the same advertisement.

Again Pfizer agreed with the Panel's suggestion as to how it could improve on making its instructions for withdrawal of advertisements more explicit to the reader. However, it was reasonable to assume that the reference to LIP 2933 would immediately alert the reader that all promotional materials bearing this code did not vary in content and were identical with the exception of the size. So whilst LIP 2933e was the journal advertisement complained about LIP2993a was an iteration of that advertisement which differed only in size to comply with the publishers' requirements.

iii) Agencies were allowed to make their own arrangements for secure storage of original artwork but the form did not require them to give details as to their arrangement for storing the original artwork.

Pfizer submitted that the form included the following statement: 'Original artwork may be kept but must be stored electronically with sufficient safeguards to ensure that it cannot be used accidentally. We suggest creating 'Withdrawn materials: not to be used'. Pfizer submitted that whilst it was responsible for communicating clearly to agencies the need to ensure that sufficient safeguards were put in place to ensure that withdrawn advertisements could not be used accidentally and even to suggest how this could be done, it could not take responsibility ultimately for the manner in which this was carried out and would have no grounds for enforcing a rule on this.

iv) The form required the recipient to confirm they had complied with the notice rather than confirm destruction of the material.

Pfizer noted that the form clearly stated that material must be destroyed and therefore confirmation of compliance with the notice meant compliance with everything stated in the notice.

Pfizer noted that in Case AUTH/2048/8/07 Grünenthal had not asked the publishers to confirm that the old version of advertisement had been destroyed. Despite this omission, the Panel did not rule a breach of Clause 9.1.

Pfizer submitted that it had, to the best of its abilities, taken all the steps required in its internal processes to comply with the undertaking signed in May 2008 and these processes were robust. This breach of undertaking had occurred because Pfizer's healthcare media company did not follow Pfizer's explicit instructions to destroy the fireman advertisement. As discussed in the previous case (Case AUTH/2048/8/07) although some improvements could be made to the 'Withdrawal of Advertisement' form, high standards had not been breached and therefore Pfizer was not in breach of Clause 9.1. Pfizer submitted that the rulings in these two cases were not consistent.

APPEAL BOARD RULING

The Appeal Board noted Pfizer's reference to Case AUTH/2048/8/07 but considered that it was not bound by the Panel's ruling in that case. Each case had to be considered on its own merits.

The Appeal Board considered that it was very important for the reputation of the industry that companies complied with their undertakings. Pfizer

had not appealed the Panel's ruling of a breach of Clause 25.

The Appeal Board noted that the 'Withdrawal of Advertisement' form sent by Pfizer to, *inter alia*, Pfizer's media buyer and Pfizer's creative design agency, stated clearly at the top that 'The following advertisements must be removed from any media in which they appear immediately. These advertisements must not be used again. The items affected are: …'. This was followed by a description of the advertisement (Lipitor fireman advertisement) a reference number, LIP 2933 and the section listing the name of the journals where it appear referred to all press as indicated in an attached document or similar. The form then stated 'Please destroy all copies of the advertisements above. Original artwork may be kept but must be stored electronically with sufficient safeguards to ensure that it cannot be used accidentally. We suggest creating a folder called "withdrawn materials: not to be used"'. The form stated that it must be signed by the recipient to confirm that they had complied with the notice and that the advertisements in the journals mentioned should not appear after 8 May 2008. The forms were signed and returned by the recipients.

The Appeal Board considered that the form made it clear that copies of the advertisement at issue were to be destroyed and not used again. The Appeal Board noted that Pfizer's media buyer had confirmed with Pfizer's healthcare media company that it would not run the Lipitor fireman advertisement again. The replacement advertisement for Lipitor had subsequently been published 34 times in October and November although not in Practitioner. The first Lipitor advertisement to appear in the Practitioner since May 2008 was in November when Pfizer's healthcare media company incorrectly published the fireman advertisement.

The Appeal Board considered that it might have been helpful if Pfizer had stated on its form that the advertisement was being withdrawn because it was in breach of the Code. Correspondence from Pfizer's healthcare media company indicated that the advertisement had been withdrawn due to out-of-date prescribing information.

Nonetheless the Appeal Board considered that Pfizer had taken reasonable steps to endeavour to comply with its undertaking; it had been badly let down by its healthcare media company. The Appeal Board did not consider in the circumstances that Pfizer had failed to maintain high standards and it thus ruled no breach of Clause 9.1. The appeal was successful.

Complaint received **15 December 2008**

Case completed **18 March 2009**

ANONYMOUS v MERCK SERONO

Promotion of Pergoveris

An anonymous, non-contactable complainant alleged that Merck Serono had encouraged its representatives to promote Pergoveris (follitropin alfa and lutropin alfa for injection) outwith its licence.

The complainant referred to two emails sent to the fertility team. The complainant stated that the first email asked the team to identify clinics that used Menopur [marketed by Ferring Pharmaceuticals Ltd] in *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles because the doctor believed in the need for luteinizing hormone (LH). The second email told the team members that they must target these IVF/ICSI cycles for use with Pergoveris. The complainant noted that Pergoveris was indicated to produce monofollicular development.

The detailed response from Merck Serono is given below.

The Panel noted that the first email referred to studies and the role of LH in improving pregnancy rates in some patients. The data suggested that LH addition was not beneficial for the unselected population but was beneficial in poor responders to FSH alone. The data for adding LH in patients over 35 was also not convincing. The email requested estimates regarding the proportion of hMG cycles that were being prescribed predominately due to belief in the positive effect of LH. This was to better target efforts with Pergoveris.

The second email referred to the need to target cycles where Menopur (hMG) was used primarily due to its LH activity leading to the use of Pergoveris in these cycles. It asked the team to focus activities on, *inter alia*, establishing Pergoveris as the recombinant alternative to u-hMG in patients who needed LH.

It appeared to the Panel from their respective summaries of product characteristics (SPCs) that there were differences between the products. Pergoveris was only indicated for use in women with severe LH and FSH deficiency; in clinical trials these patients were defined by an endogenous serum LH level <1.2 IU/L. The objective of Pergoveris therapy was to develop one follicle. Conversely there was no mention of the LH and FSH profiles for women being treated with Menopur and it could be used to induce multiple follicular development.

The Panel noted that the complainant had the burden of proving their complaint on the balance of probabilities. The complainant could not be contacted for further information. The complainant had not provided the emails which were the subject of the complaint. Merck Serono had found one and the other was of a different date to that cited by the complainant. It was not possible to ascertain whether this was indeed the email referred to by the complainant.

The Panel considered that the second email was not sufficiently clear about the differences between the products and the fact that not every patient prescribed Menopur would be suitable for Pergoveris. Pergoveris patients had to be severely LH and FSH deficient. Nonetheless, the Panel did not consider that there was sufficient evidence to show that Pergoveris had been promoted outside its marketing authorization as alleged nor had Merck Serono failed to maintain a high standard and thus no breach of the Code was ruled.

An anonymous, non-contactable complainant raised concerns about the promotion of Pergoveris (follitropin alfa and lutropin alfa for injection) by Merck Serono Limited.

COMPLAINT

The complainant asked the Authority to consider two emails sent to the fertility team on 23 May 2008 and 26 June 2008.

The complainant stated that the first email asked the team to identify clinics that used Menopur [marketed by Ferring Pharmaceuticals Ltd] in *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles because the doctor believed in the need for luteinizing hormone (LH). The second email told the team members that they must target these IVF/ICSI cycles for use with Pergoveris.

The complainant alleged that this was outside the licence for Pergoveris as it was indicated to produce monofollicular development.

When writing to Merck Serono the Authority asked it to respond in relation to Clauses 3.2 and 9.1 of the Code.

RESPONSE

Merck Serono submitted that the complainant was incorrect to state that Pergoveris was indicated for monofollicular development. The summary of product characteristics (SPC) stated 'Pergoveris is indicated for the stimulation of follicular development in women with severe LH and FSH

[follicule stimulating hormone] deficiency. In clinical trials, these patients were defined by an endogenous serum LH level <1.2IU/L'.

Prior to the launch of Pergoveris clinicians had two options to treat infertile patients with severe LH and FSH deficiency. They could use urinary derived hMG (u-hMG) or a combination of recombinant FSH and recombinant LH. The majority of these patients were treated with u-hMG as treatment could be given in a single daily injection. Pergoveris (fixed combination of 150 IU recombinant FSH and 75 IU LH) was also dosed in a single daily injection making it a logical alternative to u-hMG in patients with severe FSH and LH deficiency.

The email of 23 May 2008 asked the fertility sales team to identify fertility clinics where prescribers believed that LH supplementation was beneficial in follicular development in assisted reproduction. The team was asked to do this because prescribers that believed in the benefits of LH supplementation were likely to be interested in using Pergoveris in patients with FSH and LH deficiency. The team was also asked to quantify the number of cycles currently performed in each of these units where LH deficiency drove product choice. This was done to help them prioritise clinics where LH supplementation belief was strongest. Both these requests were consistent with the licensed indication for Pergoveris and the email did not ask the sales team to promote Pergoveris outside this indication. The email asked the team members to contact the sender if they were not clear about what they were being asked to do. All members of the team provided data in line with the request without asking for further clarification.

Merck Serono could not find an email of 26 June which matched the description outlined in the complaint but an email of 20 June might be the one referred to by the complainant although Merck Serono could not be certain.

The 20 June email aimed to clarify the sales team's objectives for the second half of 2008. One of these was to target prescribers at the clinics identified as a result of the email sent on 23 May 2008 so as to establish Pergoveris as the recombinant alternative to u-hMG in LH deficient patients. This request was consistent with the licensed indication for Pergoveris and the email did not ask the sales team to promote Pergoveris outside this indication.

In conclusion Merck Serono submitted that there had been no breach of Clauses 9.1, 3.2 or 2 of the Code.

In response to a request for further information Merck Serono referred to the licensed indication for Menopur and stated that severely LH deficient women might be candidates for either Menopur or Pergoveris.

The fertility sales team had received training from the launch of the product which emphasised the licensed indication. The initial launch presentation showed the indication on the front page and prominently in the conclusions; both reiterated that Pergoveris was limited to those women with 'severe LH and FSH deficiency'. The presentation was accompanied by two paper based materials. The product monograph gave a factual account of the trials used to support the product licence and included a copy of the SPC. The points at which the licence was emphasised were highlighted throughout the document. The sales aid supported the importance of LH and also contained the licensed indication. Both documents had been used since launch to support the key data around Pergoveris and remind the sales team of the appropriate indication.

At a meeting in July the sales team was updated on new scientific data in the morning, given an overview of sales results and shared best practice in the afternoon. The morning's discussion centred around a clinical study (Shoham *et al* 2008) on the use of recombinant LH in women with profound LH deficiency. This paper supported the use of a combination of 75 IU recombinant LH (Luveris) and 150 IU recombinant FSH (Gonal-f) in inducing follicular development in women with profound LH deficiency. The data from this study was within the licensed indication of Pergoveris and was accompanied by a briefing document which stated this fact.

In the afternoon, each member of the sales team was given the opportunity to update others on the uptake of Pergoveris at their fertility clinics. A discussion then followed on how best to increase its use by clinicians in women who were severely LH deficient. No new presentations on Pergoveris were given at this meeting. The meeting concluded with an opportunity for team members to air their views on issues they believed should be addressed in the 2009 marketing plan.

In summary, although the indications of Menopur and Pergoveris differed, the use of Menopur by a centre would indicate that it was more likely to recognise the benefits of LH as part of follicular stimulation. Therefore, identifying these centres would allow the sales team to target its efforts in the most appropriate way. This did not negate the guidance given to the sales team to promote Pergoveris within these centres only within the licensed indication which was reiterated in all materials.

PANEL RULING

The Panel noted that Pergoveris was indicated for women with severe LH and FSH deficiency. The SPC stated that in LH and FSH deficient women (hypogonadotrophic hypogonadism) the objective of Pergoveris therapy was to develop a single mature Graafian follicle from which the oocyte would be liberated after the administration of human chorionic gonadotrophin (hCG).

The Panel noted that the 23 May email referred to studies and the role of LH in improving pregnancy rates in some patients. The data suggested that LH addition was not beneficial for the unselected population but was beneficial in poor responders to FSH alone. The data for adding LH in patients over 35 was also not convincing.

The Panel noted that the 23 May email requested estimates regarding the proportion of hMG cycles that were being prescribed predominately due to belief in the positive effect of LH. This was to better target efforts with Pergoveris.

The 26 June email referred to the need to target cycles where Menopur (hMG) was used primarily due to its LH activity leading to the use of Pergoveris in these cycles. It asked the team to focus activities on, *inter alia*, establishing Pergoveris as the recombinant alternative to u-hMG in patients who needed LH.

The Panel noted that the SPC for Menopur gave a number of indications for the product which included use in women undergoing superovulation to induce multiple follicular development in patients undergoing an assisted conception technique. The SPC for Menopur also recommended that there should be at least 3 follicles greater than a defined size.

It appeared to the Panel from their respective SPCs that there were differences between the indications and uses of Pergoveris and Menopur. Pergoveris was only indicated for use in women with severe LH and FSH deficiency; in clinical trials these patients were defined by an endogenous serum LH level <1.2 IU/L. The objective of Pergoveris therapy was to develop one follicle. Conversely there was no mention of the LH and FSH profiles for women being treated with Menopur and it could be used to induce multiple follicular development.

The Panel noted that the complainant had the burden of proving their complaint on the balance of probabilities. The complainant was anonymous and non-contactable. It was thus not possible to go back for further information. The complainant had not provided the emails which were the subject of the complaint. Merck Serono had found one and the other was of a different date to that cited by the complainant. It was not possible to ascertain whether this was indeed the email referred to by the complainant.

The Panel considered that the email dated 26 June was not sufficiently clear about the differences between the products and the fact that not every patient prescribed Menopur would be suitable for Pergoveris. Pergoveris patients had to be severely LH and FSH deficient. Nonetheless, the Panel did not consider that there was sufficient evidence to show that Pergoveris had been promoted outside its marketing authorization as alleged. Thus no breach of Clause 3.2 was ruled. The Panel did not consider that Merck Serono had failed to maintain a high standard and thus no breach of Clause 9.1 was also ruled.

Complaint received **16 December 2008**

Case completed **27 January 2009**

CASE AUTH/2195/12/08

GENERAL PRACTITIONERS v OTSUKA

Conduct of representative

A general practice complained about an email sent by an Otsuka representative to the practice manager. The representative had been allowed to come to the surgery on numerous occasions and the practice was extremely distressed to find that this was how she viewed the GPs within it. She also referred to the assistant practice manager as well although not by name. The email was described as 'not appropriate' and 'intolerable' and as a direct result the practice wished to have neither the representative in question nor any other representative from Otsuka on its premises again.

The detailed response from Otsuka is given below.

The Panel was extremely concerned about the content of the email from the representative to the practice manager. The Panel noted that the representative was a personal friend of the recipient. Representatives had to be extremely careful in such circumstances to ensure that all relevant communication was appropriate. The email had been sent from one work email address to another. It addressed matters which had arisen within the recipient's practice and which were thus related to the representative's professional role. The representative had made comments about the GPs in the practice which the Panel considered were disparaging and a breach of the Code was ruled. The representative had not maintained a high standard of ethical conduct. The email was most unprofessional. Nor had the representative complied with relevant requirements of the Code. A further breach was ruled. The Panel also ruled a breach as high standards had not been maintained. The Panel noted Otsuka's acknowledgement of breaches of the Code.

With regard to Clause 2, the Panel noted that it was used as a sign of particular censure and reserved for such use. The supplementary information to Clause 2 gave examples, including when conduct of employees fell short of competent care. The Panel was extremely concerned about the email in question. The representative was acting outside company instructions but this was the company's responsibility. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.

COMPLAINT

A general practice complained about an email sent by a representative from Otsuka Pharmaceuticals (UK) Ltd to the practice manager. The representative had been allowed to come to the surgery on numerous occasions and the practice was extremely distressed to find that this was how she viewed the GPs within it. She also referred to the assistant practice manager as well although not by name.

This sort of communication was not appropriate and was intolerable.

As a direct result the practice wished to have neither the representative in question nor any other from Otsuka on its premises again.

The part of the email at issue stated:

'I am still up and working!

I was so sad to hear what hell you have being going through.

In the business that I am in. I have to deal with arseholes like this all the time! Always out for their best interest and step on anyone to achieve their goals.

Well my view point is that she has got to be shagging one of the GPs! Anyway, its shoite going through all of this, but you must remember, that you are a really good person, filled with concern and kindness for others.

I believe in Karma, what goes around comes around! She has behaved really badly. I am telling you now; this will come back to the GPs, when they wonder why they are losing money. A good practice manager needs a shit load of skills, which you have in abundance. You leaving will be a good thing in the end, as she will be so ill equipped to deal with anything from a strategic level.

I have seen this time and time again. One leaves and there the worst person ever. Another takes over, and they cannot do the job. Well GPs……. I think it may be expedient to stop here! Ha

What is the saying ? Yes……. Take heart! God you two are so young! Such an opportunity! The children are grown up……..OMG, this could turn into such an adventure for you both, you could grow your beard, buy a camper van! How ace is that!

She has done you a huge favour! Trust me!

I personally believe that we are sprits going on a human journey. I work with loads of reps and they are the most self absorbed arseholes that I have ever met in life, oh and doctors, interested in what is in it for me etc.

You must see this event as an absolute opportunity for you and your loved one to take stock and do. If you are unsure what you want to do, just sit on your own, by yourself, for as long as it takes, and it will come to you. Trust me! ……'

The email had been sent in response to an email from the practice manager requesting financial support for the purchase of medical equipment.

When writing to Otsuka, the Authority asked it to respond in relation to Clauses 2, 8.2 9.1 and 15.2 of the Code.

RESPONSE

Otsuka stated it received a copy of the complaint from the practice together with a copy of the email from its representative on 15 December. The representative had also alerted her manager to the potential for a customer complaint. The managing director was greatly disturbed to read the correspondence. To discover that a representative could behave in such a manner was extremely shocking and disappointing.

On receipt of the complaint a meeting with the representative and her line manager took place to identify and clarify the facts.

It appeared that the representative had a personal friendship with the recipient. The representative had previously worked in several practices within the area as a locum primary care manager and as such developed a close network of colleagues which she maintained after she left to work as a representative. She believed that she was conducting a personal communication by sending an email in her own time (circa 2:30am) which was intended as a message of support and which did not refer to the company, a company product or any business matters. The understanding was that the recipient was away and that their email account had been set to redirect messages in their absence, which was how the message came to the partners' attention.

The behaviour was completely out of character; the company had no reason in the past to be concerned about this representative or her performance. Recently she had a number of personal issues ongoing and these might have impaired her judgement. The company had been unable to confirm this point of view.

The representative's use of company equipment and systems to transmit her opinions was entirely unacceptable and infringed IT policy. This policy allowed incidental personal use but stated that such emails were subject to the same guidelines as business emails. It specifically prohibited the use of 'profanity, obscenity, slander or libel'. The policy was given to all staff during their company induction and they had to read and sign their agreement.

On the basis of the initial fact-finding meeting it was clear that there was sufficient information to instigate disciplinary proceedings. A formal disciplinary meeting was held, the outcome of which was that the representative was to be dismissed. However, the representative subsequently resigned.

After concluding the disciplinary proceedings and given the seriousness of the matter Otsuka wrote to the practice to apologise and express its concern over the behaviour of the representative. Otsuka advised the action taken and the resulting outcome. Otsuka received a reply accepting the prompt action and agreeing to accept representatives from the company in the future. The practice mentioned that it viewed the actions being of an individual and that the matter had been resolved with no ill feeling towards the company.

As a result of this matter the company reminded all staff of their responsibilities when using email in terms of both the Code and its own internal email policy. A copy of Otsuka's IT policy for review and further agreement had been sent to them. The company was updating this document so further training would be expected when available. This would be followed with additional Code training, with a focus on conduct and appropriate use of email.

The company was extremely disappointed about the behaviour of the individual. As an organisation it aimed to work to ethical and professional standards, in line with its Japanese heritage. Staff were carefully recruited and turnover was low. Representatives were trained on the Code during their initial training course and regularly updated. It had had no such complaints in the six years in which Otsuka had operated in the UK. Its record with regard to the Code was a good one with few complaints.

Otsuka acknowledged that the representative did not maintain high standards in breach of Clause 15.2, and, in line with its responsibilities under the Code the company accepted responsibility for this representative's actions. The representative's comments disparaged practice staff in breach of Clause 8.2. As a result of the representative's action and despite Otsuka's best efforts it acknowledged the company had failed to maintain high standards on this occasion in breach of Clause 9.1. There might have been some mitigating circumstances in this case. Nevertheless, it acknowledged, with very deep regret, that on this occasion this representative's conduct fell short of being competent care for her customers. Her actions had discredited the company and the industry in breach of Clause 2.

To conclude, Otsuka was genuinely sorry for these breaches of the Code, especially the breach of Clause 2. The actions it had taken demonstrated the level of commitment to the Code, the seriousness with which it regarded such breaches,

and that such behaviour and non-compliance would not be tolerated in Otsuka.

PANEL RULING

The Panel was extremely concerned about the content of the email from the representative to the practice manager. The Panel noted that the representative was a personal friend of the recipient. Representatives had to be extremely careful in such circumstances to ensure that all relevant communication was appropriate. The email had been sent from one work email address to another. It addressed matters which had arisen within the recipient's practice and which were thus related to the representative's professional role. The representative had made comments about the GPs in the practice which the Panel considered were disparaging and a breach of Clause 8.2 was ruled. The representative had not maintained a high standard of ethical conduct. The email was most unprofessional. Nor had the representative complied with relevant requirements of the Code. A breach of Clause 15.2 was ruled. The Panel also ruled a breach of Clause 9.1 as high standards had not been maintained. The Panel noted that Otsuka had acknowledged these breaches of the Code.

With regard to Clause 2, the Panel noted that it was used as a sign of particular censure and reserved for such use. The supplementary information to Clause 2 gave examples, including when conduct of employees fell short of competent care. The Panel was extremely concerned about the email in question. The representative was acting outside company instructions but this was the company's responsibility. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.

Complaint received **22 December 2008**

Case completed **12 February 2009**

CASE AUTH/2196/1/09

ANONYMOUS ONCOLOGIST v ASTRAZENCA

Arimidex promotional aid

An anonymous and uncontactable oncologist complained about an enclosure sent with a mailing for Arimidex (anastrozole) by AstraZeneca.

The mailing consisted of a leaflet which discussed the difficulties in telling patients that they had a recurrence of their breast cancer. Included with the leaflet was a sheet of magnetic words such as 'lump', 'spread', 'bad', 'news', 'sorry' etc which could be separated and arranged into sentences. The complainant took absolute umbrage to the utter insensitivity of what appeared to be filing cabinet or fridge magnets which could be used to spell out sentences to break bad news to patients.

Although there were no specific instructions, it was inconceivable how the use of the magnets could be in anything other than extremely poor taste. AstraZeneca appeared to suggest that instead of breaking bad news to patients through direct dialogue, the complainant should display a set of magnets in his clinic room. He would be mortified if any of his patients ever saw these items which inappropriately made light of a serious situation.

The detailed response from AstraZeneca is given below.

The Panel noted AstraZeneca's submission that the magnetic words were not intended to be a gift or a promotional aid. However, the Panel considered that they were a promotional aid. They had been sent as a wholly separate item within a promotional mailing; it was difficult to see what else they could be. They were not relevant to the practice of the recipient's profession and breaches of the Code were ruled.

The Panel noted that AstraZeneca did not expect the magnetic words to be used with patients and that they had been intended to 'grab attention and stimulate reflection'. In the Panel's view the words were more of a gimmick to make the mailing memorable; the Panel considered that their provision was demeaning to the role of the health professional. High standards had not been maintained and a breach was ruled. The Panel did not consider that the magnetic words brought discredit upon or reduced confidence in the pharmaceutical industry. Clause 2 was used as a sign of particular censure and reserved for such use.

An anonymous and uncontactable oncologist complained about a mailing (ref C15822) for Arimidex (anastrozole) sent by AstraZeneca UK Limited.

The mailing consisted of a leaflet which principally discussed the difficulties in telling patients that they had a recurrence of their breast cancer. Included with the leaflet was a sheet of magnetic words which could be separated and arranged into sentences. The words were relevant to breaking bad news about recurrence to breast cancer patients and included 'difficult', 'lump', 'spread', 'unfortunately', 'bad', 'news', 'sorry', 'cancer' etc.

A reply card offered readers the opportunity to request a copy of a survey regarding patient-physician interactions during early breast cancer treatment (Lansdown *et al*).

COMPLAINT

The complainant stated that the mailing was sent to his home address which was a mystery in itself as he did not recall having provided this to AstraZeneca.

The complainant considered that the leaflet headlined 'Dealing with recurrence is one of the most difficult aspects of breast cancer' was acceptable; it detailed the results of a survey demonstrating that physicians found telling patients that their disease had relapsed stressful and difficult.

The complainant, however, took absolute umbrage to the utter insensitivity of the enclosure ie a set of what appeared to be filing cabinet or fridge magnets with a series of detachable words which could be used to spell out sentences to break bad news to patients.

Although there were no specific instructions accompanying the magnets, it was inconceivable how the use of them could be in anything other than extremely poor taste. AstraZeneca appeared to suggest that instead of breaking bad news to patients through direct dialogue, the complainant should display a set of magnets in his clinic room. He would be mortified if any of his patients ever saw these items which inappropriately made light of a serious situation.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 2, 9.1, 18.1 and 18.2 of the Code.

RESPONSE

AstraZeneca stated that it was surprised by the complainant's proposed use of the contents of the

mailer but nevertheless sincerely regretted that this interpretation had offended him. As an ethical pharmaceutical company, AstraZeneca fully supported both the letter and spirit of the Code and aimed to maintain the highest standards at all times.

1 Use of home address

On instruction from AstraZeneca, an agency distributed the mailing to over 2,000 appropriate health professionals. AstraZeneca generated a list of names from its internal customer relations management tool. The agency also had its own database of UK health professionals. Individual's details were fully validated prior to inclusion in the database. A letter from the agency outlining its procedures for validation of its database was provided.

AstraZeneca noted that before the mailer was distributed, the complainant would have had to confirm his preference for his home address to be used for certain materials, which was the address used to distribute the mailer in question. It was understandable but unfortunate that the complainant had chosen anonymity, as his details could not be removed from the database in order to prevent further mailers being sent to his home from AstraZeneca or any of the other organizations that used the database.

2 Words mounted on a magnetic strip

It was very clear from the complainant that the enclosed leaflet was entirely acceptable including the statement that 'dealing with recurrence is one of the most difficult aspects of breast cancer'. AstraZeneca had a strong heritage in the holistic management and treatment of breast cancer and clearly understood and strongly empathized with both the sensitivity and difficulty of managing patients whose disease had sadly recurred. AstraZeneca would never seek to 'make light' of what it too believed was a very serious and challenging clinical and personal situation. On the contrary, it was because it was aware of these highly sensitive issues relating to breast cancer recurrence that AstraZeneca had funded the independently conducted survey that this mailer sought to communicate (Lansdown *et al*).

The envelope of the mailer was clearly promotional and posed the question 'When you're telling a patient her breast cancer has come back, how do you find the right words?'. This very clear, upfront question reflected the fact that 45% of physicians reported that telling a patient that her cancer had sadly returned was the worst part of the job.

The magnetic words were not intended for use with patients. Whilst AstraZeneca apologised for any offence caused, it was most surprised by the proposal that the health professional should use these words in the consulting room to make sentences to break bad news to patients, as this was absolutely not implied in the mailer. The words were intended to grab attention and stimulate reflection on which words were the most appropriate for clinicians to use following on from the question on the envelope: 'When you're telling a patient her breast cancer has come back, how do you find the right words?'. In addition, the empty quotation marks on the cover of the leaflet were clearly intended to promote further reflective thought processes.

By distributing this mailer, AstraZeneca hoped that, upon personal reflection, some clinicians would request a copy of Lansdown *et al* with an expectation that all mailer contents would then be discarded. Accounting for the Christmas break, AstraZeneca had thus far had 54 requests for the paper.

Whilst AstraZeneca conceded that this mailer, for which it apologised unreservedly, upset the recipient, it emphasised that there was absolutely no wilful intent to either offend, or to not maintain the highest of standards. AstraZeneca believed that the complainant had taken an unusual and unforeseeable interpretation of this item, which had not been replicated so far as AstraZeneca was aware by any of the other 2,000 recipients. AstraZeneca believed that the mailer addressed a very important, highly relevant and very sensitive real-life clinical situation with a quality educational offering. As such AstraZeneca could not accept and did not believe there to be any breach of Clause 9.1.

Furthermore, AstraZeneca did not accept that this mailer brought discredit upon, nor reduced confidence in, the pharmaceutical industry that benefitted particular censure. As such, it strongly refuted the accusation of a breach of Clause 2.

In relation to Clauses 18.1 and 18.2, no gift or benefit in kind had been offered. The magnetic words were not intended either as a gift or promotional aid. As stated earlier, they were included as part of the total mailing and had no value other than attempting to stimulate reflective thought. The only item that was offered was a copy of Lansdown *et al*, which was acceptable under Clause 18.4. As such, AstraZeneca did not believe there to be a breach of Clauses 18.1 or 18.2.

In summary, whilst it regretted that the mailer had offended the complainant, AstraZeneca did not believe that if had breached Clauses 18.1, 18.2, 9.1 or 2.

PANEL RULING

The Panel noted AstraZeneca's submission that the magnetic words were not intended to be a gift or a promotional aid. However, the Panel considered that they were a promotional aid. They had been sent as a wholly separate item within a promotional

mailing; it was difficult to see what else they could be. They were not relevant to the practice of the recipient's profession as required by Clause 18.2 and in that regard the Panel noted AstraZeneca's submission that it expected the contents of the mailing to be discarded. A breach of Clause 18.2, and thus also of Clause 18.1, was ruled.

The Panel noted that AstraZeneca did not expect the magnetic words to be used with patients and that they had been intended to 'grab attention and stimulate reflection'. In the Panel's view the words were more of a gimmick to make the mailing memorable. The Panel considered that the provision of the magnetic words in question was demeaning to the role of the health professional. High standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel did not consider that the magnetic words brought discredit upon or reduced confidence in the pharmaceutical industry. Clause 2 was used as a sign of particular censure and reserved for such use. The Panel ruled no breach of Clause 2.

The Panel noted AstraZeneca's response to the complainant's comments about the mailing being sent to his home. The Panel did not consider that it had a complaint under the Code in this regard. It noted that the complainant could request that his details be removed from the mailing list. However as the complainant was anonymous and non contactable there was nothing further that could be done.

Complaint received **5 January 2009**

Case completed **9 February 2009**

CASE AUTH/2197/1/09

SANOFI PASTEUR MSD v MASTA

Epaxal promotional email

Sanofi Pasteur MSD complained about an unsolicited promotional email headed 'Epaxal costings' which referred to the benefits of Epaxal Hepatitis A vaccine and was sent in October 2008 by a MASTA representative to a customer.

The detailed response from Masta is given below.

Sanofi Pasteur MSD noted that the start of the email indicated that cost related information had been requested, however the email was clearly promotional, containing six separate promotional claims (two of which could not be substantiated) and was thus unsolicited. In sending this email, which had not been through any internal approval, Masta had not maintained a high standard.

The Panel noted that Sanofi Pasteur MSD had not specified which two claims could not be substantiated. The Panel noted that the email included product claims and was promotional in nature; it did not include prescribing information and had not been certified by the company. The Panel considered that the representative had not maintained a high standard of ethical conduct and a breach of the Code was ruled as acknowledged by Masta.

Sanofi Pasteur MSD stated that during inter-company dialogue Masta had failed to assure it that its representatives had been appropriately re-briefed following its earlier complaint. The only evidence supplied was an unacceptable email from the Masta sales and marketing director to the sales team which stated:

> **'It may be worth reminding yourself of the ABPI Code of Practice which can be found at http://www.abpi.org.uk/links/assoc/PMCPA/pmcpa_code2006.pdf – not an exciting read but an important one'.**

Sanofi Pasteur MSD was concerned that this email not only cited the out-of-date version of the Code but also did not constitute adequate training on the content of the Code. Sanofi Pasteur MSD alleged that Masta had failed to train its representatives adequately on the Code. In addition, it was alleged that high standards had not been maintained.

The Panel considered that the email to the sales team was inadequate. The previous Code booklet had been provided rather than the current edition. This was most unfortunate. The Panel considered that in that regard adequate training had not been given and that high standards had not been maintained. Thus breaches of the Code were ruled.

Sanofi Pasteur MSD stated that it had previously had inter-company dialogue on a similar matter, also arising as a result of an email sent to a customer by a Masta representative which contained an exaggerated and unsubstantiated claim. As a result, a written agreement was provided by Masta in November 2007. Despite these written assurances, similar activity had reoccurred and thus Sanofi Pasteur MSD alleged that Masta was in breach of the Code.

The Panel noted that it had not previously considered a complaint regarding a Masta representative's use of email. Masta agreed that the matter currently at issue was the second time a representative had sent an email contrary to company instructions. The Panel was concerned that despite instructions following Sanofi Pasteur MSD's complaint in 2007 yet again a representative had emailed a customer with what were alleged to be exaggerated and unsubstantiated claims. Masta needed to be certain that it and its staff were clear about the requirements of the Code. The Panel considered that high standards had not been maintained in relation to the training of representatives as set out above and considered that the ruling of a breach of the Code in that point covered the allegation now before it.

Sanofi Pasteur MSD complained about an unsolicited promotional email dated 20 October 2008 which was sent by a Masta representative to a customer. The email was headed 'Epaxal costings' and referred to the benefits of Epaxal Hepatitis A vaccine.

1 Promotional, unsolicited and unapproved email

COMPLAINT

Sanofi Pasteur MSD stated that the start of the email indicated that cost related information had been requested, however the email was clearly promotional, containing six separate promotional claims (two of which could not be substantiated) and was thus unsolicited. In sending this email, which had not been through any internal approval, Masta had not maintained a high standard and was in breach of Clause 15.2.

RESPONSE

Masta agreed that the email sent by the representative was in breach of the Code.

Masta understood that the email was 'solicited',

following a discussion on Epaxal, in that the customer requested that the information discussed be reiterated in an email.

The email contained claims and was therefore promotional. The claims used in the email from the representative had not been through approval and no prescribing information was included.

Sanofi Pasteur MSD alleged that two of the claims could not be substantiated. Masta believed that the profit claim could be substantiated: the amount of profit a GP practice could make from vaccines was specific to individual practices since different discounts might be offered to different practices by the various suppliers. Consequently no general claims regarding profit could be substantiated, this however was a specific email sent to an identified practice as a follow-up to specific discussions where competitor price details might have been shared. Masta acknowledged that the email breached Clauses 4.1, 14.1, 7.2 and 7.4.

Since the above breaches were due to the activity of one individual representative who had clearly not complied with all relevant requirements Masta acknowledged a breach of Clause 15.2.

PANEL RULING

The Panel noted that Sanofi Pasteur MSD had not specified which the two claims were that it alleged could not be substantiated. Only a breach of Clause 15.2 had been alleged. The Panel noted that the email sent by the representative had included product claims and was promotional in nature; the email did not include prescribing information and had not been certified by the company. The Panel considered that the representative had not maintained a high standard of ethical conduct and a breach of Clause 15.2 was ruled as acknowledged by Masta.

2 Failure to adequately train representatives

COMPLAINT

Sanofi Pasteur MSD stated that during inter-company dialogue Masta had failed to assure it that its representatives had been appropriately re-briefed following Sanofi Pasteur MSD's complaint. The only evidence supplied was an unacceptable email to the sales team which stated:

> 'It may be worth reminding yourself of the ABPI Code of Practice which can be found at http://www.abpi.org.uk/links/assoc/PMCPA/pmcpa_code2006.pdf – not an exciting read but an important one'.

Sanofi Pasteur MSD was concerned that Masta had directed its sales team to the 2006 Code; this demonstrated a lack of awareness of the most up-to-date version. This email, particularly with the apparent lack of importance it afforded the Code, not only cited the out-of-date version of the Code but also did not constitute adequate training on the content of the Code. Sanofi Pasteur MSD alleged that Masta had failed to train its representatives adequately on the Code in breach of Clause 15.1. In addition, it was alleged that high standards had not been maintained, in breach of Clause 9.1.

RESPONSE

Masta submitted that the email sent to the team, immediately after investigating the details of this case, laid out clear and direct instruction regarding emailing of customers. If these instructions were followed no further breaches would occur.

> 'The email must be at the request of the surgery – unsolicited emails must not be sent
>
> There is no mention of any clinical or medical claims for any of our products – this essentially means that you cannot say anything about our products in any email you create
>
> There is no mention of any competitor product.
>
> If the surgery has a clinical or medical request can you forward that request to the medical department for them to answer.
>
> If you are asked to email the surgery with commercial information such as prices, discounts or delivery information can you check with your manager first before sending.'

Representatives did not need to have a detailed understanding of the nuances of all the clauses of the Code. What was important was that they had a very clear understanding of the clauses they could be in breach of through their own activities. Masta therefore believed that it was better to focus representatives on the clauses directly relevant to them. Masta representatives should not generate promotional literature or advertisements – it was better to give such dogmatic instructions on what to do and not to do than to train them on the details of the clauses which were specific to tasks they should not be doing. Counter intuitively, giving detailed training on such areas risked representatives mistakenly believing that they then knew enough about the Code to be able to produce promotional materials.

The link to the 2006 Code was a genuine error – links to the 2008 and 2006 versions appeared on the same PMCPA web page, one directly beneath the other; the 2006 link was mistakenly pasted into the document to the representatives. As explained above, Masta did not rely on representatives reading the Code to train themselves but explained in simple terms the clauses that were directly relevant. Consequently directing representatives to an old version of the Code, embarrassing though it was, did not in itself constitute a lack of adequate

training on the Code.

Masta believed its representatives were adequately trained and had sufficient scientific knowledge to enable them to provide full and accurate information about the medicines which they promoted and were not in breach of Clause 15.1.

Masta also believed that high standards must be maintained at all times. On this occasion one representative, who had failed to follow clear instruction previously provided, was the cause of this breach. Masta understood the importance of having appropriate management processes in place to ensure that every member of staff adhered to the Code. That this had failed in this instance was frustrating and Masta would explore all mechanisms to prevent this in the future, however it did not believe that this was in breach of Clause 9.1 and its understanding of how this clause was intended.

PANEL RULING

The Panel considered that the email to the sales team was inadequate. The previous Code booklet had been provided rather than the current edition. This was most unfortunate. The Panel considered that in that regard adequate training had not been given and that high standards had not been maintained. Thus breaches of Clauses 9.1 and 15.1 were ruled.

3 Persistent activity despite Masta's previous assurances

COMPLAINT

Sanofi Pasteur MSD stated that this was not the first time that representative activity of this type had been brought to its attention; previously it had had inter-company dialogue on a similar matter, also arising as a result of an email sent to a customer by a Masta representative which contained an exaggerated and unsubstantiated claim. As a result, Masta provided a written agreement on 6 November 2007. Despite these written assurances, similar activity had reoccurred and thus Sanofi Pasteur MSD alleged a breach of Clause 9.1 of the Code.

RESPONSE

Masta submitted that the steps it had taken in response to both this complaint from Sanofi Pasteur MSD and a similar previous one should be sufficient to prevent such breaches. Rapid steps were taken and clear instruction given. This was followed up individually and with the entire sales team in terms of further instruction and checks that this had been understood. The issue here was that an individual had subsequently failed to follow this instruction. Masta utilised all available management processes to prevent such breaches, with the ultimate sanction of dismissing representatives that breached the Code; such consequences served to reinforce the importance of staff adhering to the Code but could only be applied retrospectively and therefore did not serve as a fool proof method of preventing future breaches.

Masta apologised to Sanofi Pasteur MSD and to the PMCPA for this breach and sought to reassure both parties that it took the Code very seriously and that it already did, and would continue to do, everything it could to prevent any similar future issues.

PANEL RULING

The Panel noted that it had not previously considered a complaint regarding a Masta representative's use of email. Masta agreed that the matter currently at issue was the second time a representative had sent an email contrary to company instructions. The Panel was concerned that despite instructions following Sanofi Pasteur MSD's complaint to Masta in 2007 yet again a representative had sent an email to a customer with what were alleged to be exaggerated and unsubstantiated claims. Masta needed to be certain that it and its staff were clear about the requirements of the Code. The Panel considered that high standards had not been maintained in relation to the training of representatives as set out in point 2 above and considered that the ruling of a breach of Clause 9.1 in that point covered the allegation now before it.

Complaint received **9 January 2009**

Case completed **2 March 2009**

CASE AUTH/2199/1/09

NOVARTIS v ROCHE

Bondronat leavepiece

Novartis complained about a Bondronat (ibandronate) leavepiece issued by Roche. Novartis supplied Zometa (zoledronic acid). Bondronat and Zometa were both bisphosphonates which could be used to prevent skeletal events in patients with breast cancer and bone metastases.

The detailed response from Roche is given below.

Page 3 headed 'Effects of long-term therapy with bisphosphonates on the risk of developing a skeletal complication' featured three graphs comparing zoledronic acid and pamidronate, zoledronic acid and placebo and ibandronate and placebo for patients with breast cancer metastatic to bone. The primary end points for each of the three trials were given.

Novartis alleged that the graph (adapted from Body 2006) was misleading and unbalanced as it represented an indirect comparison between different studies, as data that could be directly compared on a common axis.

Novartis considered that the footnote 'NB: Caution should be exercised when using indirect comparison across trials' showed that Roche knew that the graph was inappropriate for use in promotional material. Novartis further alleged that Roche had failed to maintain the high standard of promotion expected of the pharmaceutical industry.

The Panel noted that all three graphs were contained, one below the other, within a highlighted box and each was drawn to the same scale such that the hazard ratios (x axis) lined up with each other. This was how they appeared in Body (2006) which was a review article. The three graphs compared zoledronic acid vs pamidronate (adapted from Rosen *et al* 2003), zoledronic acid v placebo (from Kohno *et al* 2005) and ibandronate (iv and oral) vs placebo (from Body *et al* 2004 and Body *et al* 2004b). To the right hand side of the boxed graphs was a short description of the primary endpoints of each study. The endpoints were not the same for each trial. The references for the four different studies were not given with the endpoints nor anywhere else on the page. Below the description of the endpoints was the statement 'NB: Caution should be exercised when using indirect comparisons across trials'. In the Panel's view this statement did not negate the incorrect implication that a direct comparison of the data was valid. Supplementary information stated that in general claims should not be qualified by the use of footnotes and the like. The final claim on the page '… the choice of a particular bisphosphonate for patients with metastatic bone disease should be based not only on efficacy but also on the risk for renal deterioration' would, in the Panel's view, further encourage direct comparison of the data from the four separate efficacy studies with different endpoints. The Panel considered that the data as shown was misleading as alleged; high standards had not been maintained. Breaches of the Code were ruled.

The claim 'Bondronat gives you renal safety reassurance' appeared as the heading to page 4 of the leavepiece and was referenced to three separate studies.

Novartis alleged that 'reassurance' was all embracing and the claim could not be substantiated, was misleading and failed to accurately reflect the Bondronat summary of product characteristics (SPC). It implied that Bondronat had no or limited renal safety concerns and further did not promote the rational use of the medicine. This was not consistent with the Bondronat SPC which detailed dose adjustments according to renal function.

The Panel considered that 'Bondronat gives you renal safety reassurance' implied that there were no renal issues with Bondronat which was not so. The dose of both iv and oral Bondronat had to be reduced in patients with severe renal impairment. The SPC for both formulations stated that, although clinical studies had shown no evidence of deterioration in renal function with long-term therapy, according to clinical assessment of the individual patient, renal function *inter alia* should be monitored in patients treated with Bondronat. With regard to adverse events the Bondronat Tablets SPC listed uraemia as an uncommon event; the SPC for Bondronat iv noted increased creatinine in 2% of patients in the phase 3 trials (n=152) and urinary retention and renal cysts as uncommon adverse events.

The Panel considered that the claim 'Bondronat gives you renal safety reassurance' appeared to be at odds with Roche's preliminary comment that it had instructed its sales force to advise health professionals to calculate creatinine clearance for every patient at the start of therapy, in addition to the monitoring required by the SPC. The Panel considered that the claim was misleading, exaggerated and could not be substantiated; it did not promote the rational use of Bondronat. Breaches of the Code were ruled.

Novartis alleged that representation of Meden *et al* and the use of a preclinical study (Body *et al*) to

support the claim 'Bondronat gives you renal safety reassurance' was unbalanced and misleading. Bullet points listed below the table [of data adapted from Meden *et al*] on page 4 were either data gathered from baseline or from an independent pre-clinical study. Novartis believed the reader would consider the bullet points to be results, or conclusions of results from the observational study. Since there was insufficient clarification of this, Novartis considered the page and bullet points misleading and ambiguous and not sufficiently complete to allow the reader to form their own opinion of the therapeutic value of medicine.

The Panel noted that page 4 detailed Meden *et al*, a poster representation of the interim analysis (n=1,704) of a running observational study which would eventually enrol 3,000 breast cancer patients with metastatic bone disease. The study had thus only enrolled 57% of its intended patients. The poster did not include any statistical analysis and the differences might not be clinically significant. There was no information to show how well matched for age, surgery etc patients who had received Bondronat previously were with those who had previously been treated with zoledronic acid. The Panel considered the data given on page 4 of the leavepiece was misleading. The study was incomplete which was not stated and claims such as 'Incidence of serum creatinine > 1.2 in zoledronic acid-treated patients was more than double that with Bondronat (26% vs 11%)' might change when the full data set was analysed. The comparisons were misleading and a breach of the Code was ruled.

Page 5 of the leavepiece, headed 'Is routine renal function monitoring performed?', included details of the interim results of a review by Houston *et al* (2008) and stated that the conclusion of the review was that the lack of routine renal function monitoring resulted in frequent overdosing with zoledronic acid.

Novartis alleged that the use of Houston *et al* was balanced and misleading. It failed to clarify that this study was a comparison of iv zoledronic acid and oral Bondronat, or the reasons for choosing these agents as adequate comparators. The study did not include a comparison with iv Bondronat.

The Panel noted Houston *et al* was a poster presentation of an interim analysis from 154 patients from a retrospective review of medical records of 200 patients; thus the interim analysis had included only 77% of the intended full data set. The poster did not include any statistical analysis and so it was impossible to know if the results of the study were clinically significant. Some of the claims taken from Houston *et al* might change on analysis of the full data set. The Panel noted that there were differences between Bondronat and zoledronic acid with regard to use in patients with renal impairment.

The Panel noted that there was no mention that Houston *et al* had compared changes in renal function in routine clinical practice with iv zoledronic acid and oral ibandronate. The results did not relate to iv Bondronat. The claims on page 5 which referred to Bondronat, however, did not differentiate between the oral or iv formulation. The Panel considered that the claims were misleading as alleged; breaches of the Code were ruled.

Novartis alleged that the bullet points on page 7 'With minimal risk of renal function concerns' and 'Time to show a good safety profile', were unbalanced, misleading and unsubstantiated. The statements also failed to adequately reflect the licence for Bondronat which required renal monitoring to make dose adjustments according to renal function. Stating that Bondronat was in effect safe was in breach of the Code.

The Panel noted that page 7 was headed 'Which bisphosphonate will you choose?' below which were two boxes of text. The left hand box read ' A bisphosphonate that requires constant monitoring and dosing adjustments to avoid risk of overdosing?' and was linked with 'or' to the second box which read 'Brondronat – an effective bisphosphonate which can be used: Irrespective of renal function; Irrespective of previous bisphosphonate history; With minimal risk of renal function concerns'. Below the boxes of text were five bullet points one of which was 'Time to show a good safety profile'.

The Panel considered that the bullet point 'With minimal risk of renal function concerns' sought to dispel any concerns that a prescriber might have about the renal safety of Bondronat. The Panel further considered that given the context in which it appeared the claim could not be substantiated; some prescribers might assume that there was no need to consider a patient's renal function either before or during therapy which was misleading. A breach of the Code was ruled.

The Panel similarly considered that, given the context in which it appeared, the claim 'Time to show a good safety profile' was misleading; a breach of the Code was ruled.

The Panel did not consider that page 7 included a claim that Bondronat was, in effect, safe as alleged. The page referred to the safety *profile* of Bondronat not just its safety; no breach of the Code was ruled

Novartis alleged that the leavepiece as a whole disparaged other companies' medicines and zoledronic acid in particular. The leavepiece inferred that Bondronat had no renal toxicity issues and by only presenting comparisons with zoledronic acid it questioned the renal safety of zoledronic acid. This was compounded by the fact that much of the comparative data was based on oral Bondronat vs iv zoledronic acid and that this was not always clear.

Novartis alleged that the leavepiece presented such a serious issue as to be in breach of Clause 2. There

were multiple breaches of the Code and attempts to disparage zoledronic acid. There was a failure to maintain the high standards expected in the promotion of medicines because of this. This discredited the pharmaceutical industry and reduced confidence in the industry.

Although noting its rulings above, on balance the Panel did not consider that overall the leavepiece had disparaged zoledronic acid or the activities of other pharmaceutical companies as alleged; no breach of the Code was ruled.

The Panel further did not consider that the leavepiece brought discredit upon or reduced confidence in the pharmaceutical industry as alleged. No breach of Clause 2 was ruled. Clause 2 was a sign of particular censure and reserved for such.

Novartis Pharmaceuticals UK Ltd complained about a leavepiece (ref P116532) for Bondronat (ibandronate) issued by Roche Products Limited. Novartis supplied Zometa (zoledronic acid). Bondronat and Zometa were both bisphosphonates which could be used to prevent skeletal events in patients with breast cancer and bone metastases.

Preliminary comments by Roche

Roche stated that it withdrew the leavepiece in November 2008 to update the prescribing information, however the claims at issue had been used in subsequent materials and so Roche had defended them through dialogue with Novartis. The leavepiece was used by the Bondronat hospital sales force with clinical and medical oncologists (consultants and specialist registrars) who treated metastatic breast cancer and also with breast care nurses.

Roche explained that bone metastases occurred in up to 75% of patients with metastatic breast cancer and such patients survived an average of 2.5 years from diagnosis of bone metastases. These patients required treatment to palliate bone pain and to reduce skeletal related events such as fractures, spinal cord compression and the need for surgery or radiotherapy to affected bones. Bisphosphonates reduced both the skeletal related events and pain associated with bone metastases. Although most patients did not undergo cytotoxic anticancer therapy continuously, bisphosphonate therapy was usually continued from the diagnosis of bone metastases until decline in performance status or death. Some patients however, had intermittent bisphosphonate therapy, as needed to control bone pain. This prolonged duration of therapy meant that many bisphosphonate patients might have some level of renal impairment, as a result either of their underlying disease or of their prior treatments (Body *et al* 2005). A recent large observation study of bisphosphonates in routine clinical practice showed some degree of renal impairment in up to 29% of patients (Meden *et al* 2007).

In man, up to 60% of the bisphosphonate reaching the circulation was rapidly bound to bone, while the remainder was eliminated unchanged by the kidneys, such elimination might occur more slowly in patients with low creatinine clearance, allowing medicine to accumulate. High doses accompanied by high molar concentrations of some bisphosphonates had been shown to overload the renal elimination mechanism and the retained medicine could damage renal cells (Body *et al* 2005). This was more likely to occur in renally impaired patients, where medicines were cleared more slowly. Under phase III clinical trial conditions renal toxicity was an infrequent, but potentially very serious, side-effect associated with the administration of intravenous (iv) bisphosphonates. The acute renal failure associated with iv bisphosphonate administration might be clinically reversible, but varying degrees of irreversible impairment might persist and eventually lead to chronic renal failure (Tanvetyanon and Stiff 2006). The level of renal side-effects seen in clinical trials differed between the various bisphosphonates and might be related to different renal half-lives (Body *et al* 2005). Thus Section 4.4 of the iv Bondronat summary of product characteristics (SPC) stated 'Clinical studies have not shown evidence of deterioration in renal function with long term Brondronat therapy', but Section 4.4 of the iv zoledronic acid SPC stated 'renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of Zometa'. There were also instructions in the SPC for many bisphosphonates used in metastatic bone disease to reduce the dose in patients with renal impairment because of the increased accumulation in such patients. However, the recommended dose reductions were different for the various bisphosphonates.

Market research amongst 90 UK consultants and specialist registrars showed that they ranked side-effects as second in importance only to efficacy when prescribing bisphosphonates (Healthcare Partners, 2006). However, Roche knew from individual consultant oncologists and from an audit of clinical practice across four large UK teaching hospitals, that in a number of UK centres creatinine clearance was not routinely calculated for patients undergoing bisphosphonate therapy (Houston *et al* 2008). As the recommended dose reductions for bisphosphonates were based on creatinine clearance, a lack of routine creatinine clearance calculation was of considerable concern. Accordingly Roche had instructed its Bondronat sales force to advise health professionals to calculate creatinine clearance for every patient at the start of Bondronat therapy, in addition to the monitoring required by the SPC.

Bisphosphonates were available in both iv and oral formulations and overall in UK hospitals in 2008, 3% of breast cancer patients with metastatic bone disease received oral clodronate, 17% iv pamidronate, 35% Bondronat oral/iv and 44% iv zoledronic acid (IMS, Oncology Analyser, Sep 08).

Amongst breast cancer patients treated with iv bisphosphonates, the level of Bondronat usage in UK hospitals rose from 2% in 2007 to 6% in 2008 (IMS, Oncology Analyser, Sep 08).

The leavepiece sought to remind health professionals of this important area of patient safety and to help them to consider whether their routine clinical practice was sufficient to ensure best practice in the safe prescribing of bisphosphonates.

1 Page 3, graph of three studies, adapted from Body (2006)

The page was headed 'Effects of long-term therapy with bisphosphonates on the risk of developing a skeletal complication'. It included three graphs comparing zoledronic acid and pamidronate, zoledronic acid and placebo and ibandronate and placebo for patients with breast cancer metastatic to bone. The primary end points for each of the three trials featured were given.

COMPLAINT

Novartis alleged that the graph (adapted from Body 2006) was misleading and unbalanced in breach of Clauses 7.2, 7.3 and 7.8. The graph represented an indirect comparison between different studies, as data that could be directly compared on a common axis.

Novartis was not satisfied that Roche's response that the footnote 'NB: Caution should be exercised when using indirect comparison across trials' was sufficient to negate its alleged breaches of the Code.

Novartis considered that the footnote showed that Roche knew that use of the graph in this way was inappropriate in promotional material. Novartis further alleged a breach of Clause 9.1 as Roche had failed to maintain the high standard of promotion expected of the pharmaceutical industry.

RESPONSE

Roche submitted that, as mandated by the supplementary information to Clause 7.8, the graph had been faithfully reproduced from the original publication, with the only change being to substitute the full names of the various medicines, rather than the abbreviations used in the original. The graph showed a relevant and substantiable feature of three medicines used for the same intended purpose and no trade names were used. The graph was not misleading as it showed pre-planned analyses of the risk of skeletal complications from all the studies, without any distortion, exaggeration or undue emphasis. In addition, the page clearly stated the primary efficacy endpoint for each study, in order not to mislead the reader. The statement 'NB: Caution should be exercised when using indirect comparisons across trials' was not a footnote; it was in the same size typeface as other explanatory notes about the studies and italicised in order to bring it more clearly to the reader's attention.

Roche submitted that the graph was not in breach of Clauses 7.2, 7.3 or 7.8, nor was it inappropriate to use it in promotional material and as it did not constitute a failure to maintain high standards in promotion. Roche denied a breach of Clause 9.1.

PANEL RULING

The Panel noted that three graphs on page 4 showed the effects of long-term therapy with bisphosphonates on the risk of developing a skeletal complication. All three graphs were contained, one below the other, within a highlighted box and each was drawn to the same scale such that the hazard ratios (x axis) lined up with each other. This was how they appeared in Body (2006) which was a review article.

The three graphs compared zoledronic acid vs pamidronate (adapted from Rosen *et al* 2003), zoledronic acid v placebo (from Kohno *et al* 2005) and ibandronate (iv and oral) vs placebo (from Body *et al* 2004 and Body *et al* 2004b). To the right hand side of the boxed graphs was a short description of the primary endpoints of each study. The endpoints were not the same for each trial. The references for the four different studies were not given with the endpoints nor anywhere else on the page. Below the description of the endpoints was the statement 'NB: Caution should be exercised when using indirect comparisons across trials'. In the Panel's view this statement did not negate the incorrect implication that a direct comparison of the data was valid. The supplementary information to Clause 7 stated that in general claims should not be qualified by the use of footnotes and the like. The final claim on the page was a quotation referenced to Body *et al* (2005) that '… the choice of a particular bisphosphonate for patients with metastatic bone disease should be based not only on efficacy but also on the risk for renal deterioration'. In the Panel's view this would further encourage direct comparison of the data from the four separate efficacy studies with different endpoints. The Panel considered that the data as shown was misleading as alleged. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

2 Claim 'Bondronat gives you renal safety reassurance'

This claim appeared as the heading to page 4 of the leavepiece and was referenced to Body *et al* (2003), Body *et al* (2004b) and McLachlan *et al* (2006). Data from an observational study in 1,704 patients from Meden *et al* (2007) was given.

COMPLAINT

Novartis submitted that 'reassurance' was all embracing and the claim as a whole could not be substantiated in light of the totality of clinical evidence on Bondronat, despite the statement being referenced. The claim was misleading and failed to accurately reflect the Bondronat SPC. The claim implied that Bondronat had no or limited renal safety concerns and further did not promote the rational use of the medicine in breach of Clause 7.10. This was not consistent with Section 4.2 of the Bondronat SPC which gave clear dose adjustments according to measures of renal function. Novartis alleged breaches of Clauses 7.2 and 7.4.

RESPONSE

Roche stated that it chose the verb to 'reassure' because it meant to 'restore confidence to' or 'dispel the apprehensions of'. The title on page 4, referenced to the clinical trials for Bondronat in breast cancer patients with metastatic bone disease, which showed levels of renal impairment similar to those in placebo patients, undertook to dispel a clinician's apprehension about the renal safety of Bondronat. The SPC for both iv and oral Bondronat stated in Section 4.4 'Clinical studies have not shown evidence of deterioration in renal function with long term Bondronat therapy'. Section 4.2 of the SPC for iv Bondronat also stated 'There is no evidence of a reduction in tolerability associated with an increase in exposure to ibandronate in patients with various degrees of renal impairment'. These statements and the published clinical trials for Bondronat should reassure prescribers that there were very limited renal safety concerns associated with Bondronat therapy. The recommendation in the SPCs to reduce the dose of both oral and iv Brondronat in patients with several renal impairment (creatinine clearance <30ml/min) was a pharmacokinetic consideration rather than one of tolerability (as indicated above, bisphosphonates were excreted primarily via the kidney). It did not suggest that there was evidence of renal damage with Bondronat, but that these reduced doses were more appropriate for patients with limited renal function who might therefore maintain a higher level of the medicine. The claim was thus not inaccurate, it was balanced, objective and capable of substantiation and therefore not in breach of Clauses 7.2 and 7.4. This claim was also not in breach of Clause 7.10 as it did not exaggerate, as shown by the statements from the SPCs and it contained no superlatives.

PANEL RULING

The Panel considered that 'Bondronat gives you renal safety reassurance' implied that there were no renal issues with Bondronat which was not so. The dose of both iv and oral Bondronat had to be reduced in patients with severe renal impairment (creatinine clearance < 30ml/min). The SPC for both formulations contained the recommendation in Section 4.4 special warnings and precautions for use that, although clinical studies had shown no evidence of deterioration in renal function with long-term therapy, according to clinical assessment of the individual patient, renal function *inter alia* should be monitored in patients treated with Bondronat. With regard to adverse events the Bondronat Tablets SPC listed uraemia as an uncommon event; the SPC for Bondronat iv noted increased creatinine in 2% of patients in the phase 3 trials (n=152) and urinary retention and renal cysts as uncommon adverse events.

The Panel considered that the claim 'Bondronat gives you renal safety reassurance' appeared to be at odds with Roche's preliminary comment that it had instructed its sales force to advise health professionals to calculate creatinine clearance for every patient at the start of therapy, in addition to the monitoring required by the SPC. The Panel considered that the claim was misleading and exaggerated; it did not promote the rational use of Bondronat. Breaches of Clauses 7.2 and 7.10 were ruled. The claim was not capable of substantiation. A breach of Clause 7.4 was ruled.

During its consideration of the matter, the Panel noted that Clause 7.9 of the Code required that the word 'safe' must not be used without qualification. The supplementary information to Clause 7.9 stated that the restrictions on the word 'safe' applied equally to grammatical derivatives of the word such as 'safety' and noted that phrases such as 'demonstrated safety' and 'proven safety' would be prohibited under Clause 7.9. The Panel requested that, although the claim at issue had been ruled in breach of other clauses of the Code, both parties be reminded of the requirements of Clause 7.9.

3 Inappropriate representation of data (Meden *et al*) to support the claim 'Bondronat gives you renal safety reassurance' and subsequent bullet points on page 4

COMPLAINT

Novartis alleged that representation of Meden *et al* and the use of a preclinical study (Body *et al*) to support the claim 'Bondronat gives you renal safety reassurance' was unbalanced and misleading. The bullet points listed below the table [of data adapted from Meden *et al*] were either data gathered from baseline, or from an independent pre-clinical study. Novartis believed the reader would consider the bullet points to be results, or conclusions of results from the observational study. Since there was insufficient clarification of this, Novartis considered the page and bullet points were misleading and ambiguous and not sufficiently complete to allow the reader to form their own opinion of the therapeutic value of medicine. Without clarification of inter-patient group factors that might have influenced the baseline readings or a statistical analysis allowing interpretation of the data this information also prevented the reader from drawing their own opinion

of the validity of the claim. Novartis alleged that this data did not support the claim, and that the way it was presented breached Clauses 7.2 and 7.3.

RESPONSE

Roche submitted that Meden *et al* represented a large and powerful collection of data from routine clinical practice, which gave clinicians a more realistic view of the range of patients who might enter their everyday oncology clinic than could be see in a phase III trial. The sometimes intermittent nature of bisphosphonate therapy to control bone pain meant that some patients requiring bisphosphonates might have received them previously. The fact that fewer patients treated with Bondronat (iv or oral) prior to study entry showed some degree of renal impairment (glomerular filtration rate, as measured by creatinine clearance, ≤50ml/min) than in the groups of patients pre-treated with the other 3 bisphosphonates, substantiated the claim. The first three bullet points below referred to the same dataset. This was neither misleading nor ambiguous. The study on page 4, by showing baseline renal function of patients commencing a course of bisphosphonate therapy, provided important data for clinicians considering prescribing bisphosphonates. These data and their presentation were not misleading, ambiguous, distorted or exaggerated and did not breach Clauses 7.2 or 7.3.

PANEL RULING

The Panel noted that page 4 detailed Meden *et al*. The cited reference was a poster presented at an international breast cancer symposium held in the US. The poster presented the interim analysis (n=1,704) of a running observational study which would eventually enrol 3,000 breast cancer patients with metastatic bone disease. The study had thus only enrolled 57% of its intended patients. The poster did not include any statistical analysis and the differences might not be clinically significant. There was no information to show how well matched for age, surgery etc patients who had received Bondronat previously were with those who had previously been treated with zoledronic acid. The Panel considered the data given on page 4 of the leavepiece was misleading. The study was incomplete which was not stated and claims such as 'Incidence of serum creatinine > 1.2 in zoledronic acid-treated patients was more than double that with Brondronat (26% vs 11%)' might change when the full data set was analysed. The comparisons were misleading and breaches of Clauses 7.2 and 7.3 were ruled.

4 Question 'Could many bisphosphonate patients be receiving too high a dose?' and the following bullet points and conclusion

Page 5 of the leavepiece was headed 'Is routine renal function monitoring performed?' It included details of the interim results of a review by Houston *et al* (2008) and stated that the conclusion of the review was that the lack of routine renal function monitoring resulted in frequent overdosing with zoledronic acid.

COMPLAINT

Novartis alleged that the use of Houston *et al* was unbalanced and misleading in breach of Clauses 7.2 and 7.3. It failed to clarify that this study was a comparison of iv zoledronic acid and oral Bondronat, or the reasons for choosing these agents as adequate comparators. As this study did not include a comparison with iv Bondronat, Novartis believed this further added to its allegation that Roche attempted to use misleading data and a lack of balance in its description to validate points or statements within promotional material.

RESPONSE

Roche noted that page 5 outlined the interim results of an audit of bisphosphonate therapy undertaken in a number of NHS hospitals. The page reinforced the message that patients might have some degree of renal impairment prior to starting bisphosphonate therapy and to show that in some UK centres routine monitoring of renal function was not sufficient to prevent overdosing of some patients. When Roche knew the interim results of Houston *et al* prior to publication, it not only instructed its sales force to advise health professionals to calculate creatinine clearance for every patient at the start of Bondronat therapy, but it also shared these results with Novartis to make it aware of data which might have an impact on patient safety.

The two bisphosphonates included in the audit, iv zoledronic acid and oral Bondronat, were those most commonly used in UK hospitals and they reflected the prescribing habits of the clinicians involved in the audit. Intravenous Bondronat was not included as it was not used in the hospitals which undertook this study, reflecting its low share of the UK iv bisphosphonate market (2% in 2007). However, if iv Bondronat had been included the conclusion might have been very similar. The SPCs for both oral and iv Bondronat stated that 'according to clinical assessment of the individual patient, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with Bondronat'. Dose reduction of either oral or iv Bondronat was recommended only for patients with severe impairment (creatinine clearance <30 ml/min). In contrast, the zoledronic acid SPC recommended measurement of serum creatinine prior to each dose and dose reduction was recommended in both mild and moderate renal impairment (creatinine clearance ≥ 30 to ≤ 60 ml/min). Zoledronic acid was not recommended for use in patients with severe

renal impairment and the SPC also recommended that treatment be withheld if renal function had deteriorated (ie a serum creatinine increase of 0.5mg/dl in patients with normal (<1.4mg/dl) baseline values and 1.0mg/dl where baseline was abnormal). The difference in renal monitoring and dose reduction requirements for zoledronic acid and Bondronat led to the different conclusions about overdosing of the two medicines in this audit. The data presented on page 5 referred to substantiable features of two medicines used for the same intended purpose, did not show a lack of balance and was not misleading. Roche denied breaches of Clauses 7.2 or 7.3.

During the inter-company dialogue with Novartis, Roche agreed to quote the recommendation for renal function monitoring from the Bondronat SPC in this piece and this had now been added to Roche's materials.

PANEL RULING

The Panel noted that page 5 detailed Houston *et al*, an interim analysis from 154 patients presented as a poster at an international meeting. The study involved a retrospective review of medical records of 200 patients thus the interim analysis had included only 77% of the intended full data set. The poster did not include any statistical analysis and so it was impossible to know if the results of the study were clinically significant. Some of the claims taken from Houston *et al* might change on analysis of the full data set. The Panel noted that there were differences between Bondronat and zoledronic acid with regard to use in patients with renal impairment.

The Panel noted that there was no mention that Houston *et al* had compared changes in renal function in routine clinical practice with iv zoledronic acid and oral ibandronate. The results did not relate to iv Bondronat. The claims on page 5 which referred to Bondronat, however, did not differentiate between the oral or iv formulation.

The Panel considered that the claims were misleading as alleged. Breaches of Clauses 7.2 and 7.3 were ruled.

5 Question 'Which bisphosphonate will you choose' on page 7 and the subsequent information on that page.

COMPLAINT

Novartis stated that the bullet point in the highlighted box for Bondronat 'With minimal risk of renal function concerns' along with the second bullet point below the linked boxes, 'Time to show a good safety profile', was unbalanced, misleading and unsubstantiated by the evidence provided in breach of Clause 7.2. The statements also failed to adequately reflect the licence for Bondronat which required renal monitoring to make dose adjustments according to renal function (Sections 4.2 and 4.4 of the iv and oral Bondronat SPCs respectively). Stating that Bondronat was in effect safe was in breach of Clause 7.9.

RESPONSE

Roche submitted that the bullet point 'With minimal risk of renal function concerns' was referenced to the data from the large observational study (Meden *et al*) in which patients given prior Bondronat showed no greater incidence of renal impairment than those who were bisphosphonate naïve. This large study of patients in routine clinical practice verified the statements about renal safety in Sections 4.2 and 4.4 of the Bondronat SPC and substantiated the bullet point on page 7. The bullet point 'Time to show a good safety profile' referred to the long-term follow up data over 4 years of Bondronat therapy, which showed a very low level of adverse events and substantiated the 'good safety profile' (McLachlan *et al* 2006). These bullet points were not unbalanced or misleading as they represented the available data. As discussed above, the recommendation in the SPCs to reduce the dose of oral and iv Bondronat in patients with severe renal impairment was not a suggestion that there was any evidence of renal damage with Bondronat and so this did not conflict the bullet points on page 7. This same page also neither claimed nor implied that Bondronat was safe; it referred the reader to the long-term safety profile and suggested there was a 'minimal risk' of renal function concerns. This page was fully referenced, was balanced and capable of substantiation, was not misleading and did not claim that Bondronat was safe. It compared material and relevant features of Bondronat with a medicine for the same intended purpose. It was not in breach of Clauses 7.2 or 7.9.

PANEL RULING

The Panel noted that page 7 was headed 'Which bisphosphonate will you choose?' below which were two boxes of text. The left hand box read ' A bisphosphonate that requires constant monitoring and dosing adjustments to avoid risk of overdosing?' and was linked with 'or' to the second box which read 'Brondronat – an effective bisphosphonate which can be used: Irrespective of renal function; Irrespective of previous bisphosphonate history; With minimal risk of renal function concerns'. Below the boxes of text were five bullet points one of which was 'Time to show a good safety profile'.

The Panel considered that the bullet point 'With minimal risk of renal function concerns' sought to dispel any concerns that a prescriber might have about the renal safety of Bondronat. The Panel further considered that given the context in which it appeared the claim could not be substantiated; some prescribers might assume that there was no

need to consider a patient's renal function either before or during therapy which was misleading. A breach of Clause 7.2 was ruled.

The Panel similarly considered that, given the context in which it appeared, the claim 'Time to show a good safety profile' was misleading. A breach of Clause 7.2 was ruled.

The Panel did not consider that page 7 included a claim that Bondronat was, in effect, safe as alleged. The page referred to the safety profile of Bondronat not just its safety. No breach of Clause 7.9 was ruled

6 The leavepiece as a whole

COMPLAINT

Novartis alleged that the leavepiece when considered as a whole disparaged other companies' medicines and zoledronic acid in particular in breach of Clause 8.1. Throughout the piece there was the story that Bondronat had no renal toxicity issues but that other bisphosphonates had. However the only comparator used was zoledronic acid and the aim of the leavepiece was to question the renal safety of zoledronic acid particularly and to state or suggest Bondronat had no renal toxicity issues. Questions like 'Are you confident your choice of bisphosphonate is not putting patients at risk of renal damage?' and statements like 'the choice of a particular bisphosphonate for patients with metastatic bone disease should be based not only on efficacy but also the risk for renal deterioration' and 'Could many bisphosphonate patients be receiving too high a dose?' clearly attempted to disparage iv zoledronic acid. This was compounded by the fact that much of the comparator data was based on oral Bondronat vs iv zoledronic acid and that this was not always clear from the statements and data presented.

Finally, Novartis alleged that the leavepiece, as a whole, presented such a serious issue as to be in breach of Clause 2. Within its 8 pages there were multiple breaches of Clause 7 and attempts to disparage zoledronic acid. There was a clear failure to maintain the high standards expected in the promotion of medicines because of this and because of the inappropriate use of studies. Even more serious there were points which disparaged health professionals and questioned their judgement and opinions. The use of data inappropriately with the potential to mislead prescribers and promote the irrational use of Bondronat that might lead to its use outside the product's licence (see Section 4.2 of the SPC and the need for dose adjustments for patients with renal deterioration) leading to very serious patient safety concerns. Also recognising the responses received from Roche in inter-company dialogue there seemed to be little understanding or recognition of the requirements of the Code. This as a whole discredited the pharmaceutical industry and reduced confidence in the industry.

Novartis noted that Roche made much of the fact that many of the statements in the leavepiece were questions which allowed a representative to introduce the piece and initiate discussion. Novartis was concerned that Roche's position in presenting such unbalanced information in the style and format of this leavepiece raised concerns as to what representatives were briefed to say in their ongoing discussions. Novartis therefore considered that the briefing material to sales representatives on how to use this leavepiece should also be central to the Authority's consideration of the balance of this piece.

RESPONSE

Roche submitted that Novartis' allegation that the leavepiece disparaged other companies' medicines and sought to question the renal safety of zoledronic acid in particular, was unfounded. The leavepiece used accurate and balanced comparisons of Bondronat with other medicines which were prescribed for the same intended purpose. The piece raised the question of whether sufficient renal function monitoring was performed in order to administer both Bondronat and zoledronic acid at the doses recommended in their SPCs. It did not seek to exaggerate the difference between the medicines, by setting out aspects of those SPCs. For example, although Section 4.4 of the SPC for Bondronat stated 'Clinical studies have not show evidence of deterioration in renal function with long term Bondronat therapy' and Section 4.4 of the zoledronic acid SPC stated 'renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a singe dose of Zometa', Roche did not believe it was appropriate to include such statements in the piece.

Novartis also suggested that the leavepiece sought to show that Bondronat alone had no renal toxicity issues, while other medicines did. However, the piece neither claimed, nor attempted to give the impression that there was no renal toxicity with Bondronat and Roche showed clearly, on page 6 of the piece, that the iv dose should be given more slowly in mild renal impairment and both iv and oral doses should be reduced in severe renal impairment.

Novartis also complained that there was a lack of clarity about where oral Bondronat was compared with iv zoledronic acid. In terms of the requirement for renal monitoring and dose reduction for renal impairment, the SPC for oral and iv Bondronat were identical and for both formulations the same statement about lack of 'evidence of deterioration in renal function' was included in the SPC. Therefore in this leavepiece, with its emphasis on renal safety, renal monitoring and dose reductions, it was immaterial whether the data were generated with oral or iv Bondronat although the former was, with iv zoledronic acid, the most frequently used

bisphosphonate in UK hospitals. Roche therefore rejected the allegation of a breach of Clause 8.1.

Novartis also suggested that the leavepiece represented such a serious issue that it was in breach of Clause 2. This was based on the numerous alleged breaches of Clause 7 in the piece, the inappropriate use of studies and disparagement of prescribers and attempts to promote the use of Bondronat outside its product licence, leading to serious patient safety concerns. Roche believed it had shown, in the points above, that none of the alleged breaches of Clause 7 could in fact be substantiated. Moreover, the leavepiece did not disparage prescribers; the only statement which questioned prescribing habits 'lack of routine renal function monitoring results in frequent overdosing with zoledronic acid' (page 5) was a direct quotation from Houston *et al*, and used at the very specific request of the author who was a UK opinion leader in the use of bisphosphonates in metastatic breast cancer. Roche had not attempted to promote the use of Bondronat outside its licence in breast cancer patients with bone metastates and it clearly showed, in the table on page 6, the dosing recommendations for patients with all grades of renal impairment.

Roche took its obligations to ensure the renal safety of patients treated with Bondronat extremely seriously, as witnessed by instructions to its field force to recommend that clinicians monitored renal function in all patients before therapy. This instruction was made when Roche knew that the interim results of Houston *et al* demonstrated a lack of renal monitoring in routine practice in some centres. Had Roche not acted promptly to try and ensure adequate monitoring of Bondronat patients and had it not also brought the lack of renal function monitoring to Novartis's attention, it might be possible to suggest that Roche's conduct was likely to endanger patient safety and bring the industry into disrepute. However, in the present case and with regards to the disputed leavepiece, Roche categorically rejected the allegation of a breach of Clause 2.

PANEL RULING

Although noting its rulings above, on balance the Panel did not consider that overall the leavepiece had disparaged zoledronic acid or the activities of other pharmaceutical companies as alleged. No breach of Clause 8.1 was ruled.

The Panel further did not consider that the leavepiece brought discredit upon or reduced confidence in the pharmaceutical industry as alleged. No breach of Clause 2 was ruled. Clause 2 was a sign of particular censure and reserved for such.

Complaint received **13 January 2009**

Case completed **4 March 2009**

CASE AUTH/2201/1/09

ASTRAZENECA v NOVARTIS

Femara press release

AstraZeneca alleged that the title of a Novartis UK press release, 'Femara (letrozole) FIRST aromatase inhibitor to indicate OVERALL SURVIVAL BENEFIT versus tamoxifen when taken for five years after breast cancer surgery' was misleading as it exaggerated study results (Breast International Group (BIG) 1-98 study) which had failed to show statistical significance (p=0.08).

AstraZeneca noted that consumer journalists were able to access the press release online and the outputs were most likely to be read by the public. The press release raised unfounded hopes of increased survival that could not be substantiated by the current evidence. Patients reading this information would be encouraged to demand letrozole over other aromatase inhibitors. There was no evidence of survival benefit for any aromatase inhibitor used in this setting.

AstraZeneca alleged that the intention of the headline to mislead readers into believing letrozole had achieved a survival benefit over tamoxifen was further evidenced by the quotation in the press release by a senior company spokesman that 'The survival data shown may offer new promise for breast cancer patients'. All aromatase inhibitors had shown benefits in disease-free survival in the adjuvant setting. However there was no 'new promise' for these patients. Based on these data it would still be inappropriate for health professionals to counsel their patients on the 'promise' of a survival benefit from any aromatase inhibitor, letrozole included.

AstraZeneca was further concerned by the statement 'Long-term follow-up from major, independent BIG 1-98 trial adds further evidence that starting with Femara may be the optimal treatment strategy versus *tamoxifen*' (emphasis added). There was no new evidence from this analysis that suggested this was the case. Novartis had tried to use a non-significant survival benefit to suggest that letrozole was superior to anastrozole (AstraZeneca's product Arimidex), the only other licensed aromatase inhibitor in this setting. This was incorrect as neither had shown a statistically significant overall survival benefit in the adjuvant setting. Patients reading this information would be encouraged to demand letrozole over other aromatase inhibitors.

AstraZeneca stated that the press release referred to a separate censored analysis, which was 'in favour' of letrozole, but did not clearly state that the analysis was not protocol defined and performed *post hoc* in a population that had been un-blinded, which severely limited the ability to assess the significance of the result. This was further evident in the slides from the presentation of the data which did not refer to event numbers, nor to a p value. The press release did not make clear any of the caveats of this analysis, further misleading readers as to the robustness of the data.

During inter-company dialogue Novartis suggested it qualified the statement by adding a non-significant p value. However the consumer media could not be expected to understand the subtleties of complex data and it could potentially mislead readers eg a Daily Mail article clearly stated that letrozole reduced the risk of death by 20% but did not state that the results were non-significant. The article would encourage patients to demand a specific aromatase inhibitor. A non-significant survival result did not justify providing information to the public in this manner. AstraZeneca alleged that Novartis had failed to maintain high standards, and press releases of this nature brought discredit to, and reduced confidence in, the pharmaceutical industry.

The detailed response from Novartis is given below.

The Panel noted the results from the new data. The reduced risk of death for Femara vs tamoxifen was not statistically significant (p= 0.08) in the intention to treat analysis. The Panel considered that the heading to the press release that Femara was the '… FIRST aromatase inhibitor to indicate OVERALL SURVIVAL BENEFIT versus tamoxifen… ' was not a fair reflection of the study results; it gave the clear impression that a clinically significant difference had been established between the products which was not so. The Panel did not consider that the use of the word 'indicate' negated the otherwise misleading impression as submitted by Novartis. The Panel considered that the heading was misleading as alleged and a breach of the Code was ruled.

The Panel considered that the press release raised unfounded hopes of successful treatment and would in effect encourage patients to ask for a specific prescription only medicine, Femara, as alleged. A breach of the Code was ruled.

With regard to the claim 'Long-term follow-up from major independent BIG 1-98 trial adds further evidence that starting with Femara may be the optimal treatment strategy versus tamoxifen' the Panel noted that there were no clinical studies comparing Femara and anastrozole. There were treatment strategies other than Femara. The Panel

considered that the press release did not make this sufficiently clear. In the Panel's view the use of the phrase 'may be' did not negate the impression that Femara was the optimal treatment strategy vs tamoxifen. The Panel considered that patients would be inclined to ask for Femara in preference to other aromatase inhibitors. The Panel considered that the claim in question was misleading in this regard and a breach of the Code was ruled.

The statement 'To explore the impact of the selective crossover, an additional analysis was conducted censoring follow-up times at the date of crossover to letrozole for 25% of the patients in the tamoxifen arm. In this analysis a 19% reduction in risk of death (HR 0.81, 95% CI: 0.69-0.94) was observed in favour of Femara' did not in the Panel's view reflect the nature of the data. This analysis was not protocol defined and was performed *post-hoc* with the tamoxifen arm un-blinded. The Panel considered the statement was misleading as insufficient detail was provided about the nature of the data. A breach of the Code was ruled. In the Panel's view the Daily Mail article provided by AstraZeneca to support its complaint demonstrated that the press release was misleading.

The Panel did not consider that it was a breach of the Code *per se* to issue a press release about non-significant survival results and on this narrow point no breach of the Code was ruled.

The Panel was concerned that a misleading press release had been issued about data that would be of great interest to the public and health professionals. High standards had not been maintained and a breach of the Code was ruled.

With regard to the alleged breach of Clause 2 the Panel considered it was very important that press releases, particularly those that were made available to consumer journalists about sensitive issues such as survival in cancer patients, were fair, factual and not misleading. Clause 2 was used as a sign of particular censure and reserved for such use. The Panel considered that the circumstances warranted such a ruling and a breach of Clause 2 was ruled.

AstraZeneca UK Limited complained about a UK press release (ref FEM08000117) issued by Novartis Pharmaceuticals UK Ltd. The press release dated 11 December, was headed 'Femara (letrozole) FIRST aromatase inhibitor to indicate OVERALL SURVIVAL BENEFIT versus tamoxifen when taken for five years after breast cancer surgery'.

The press release referred to results released that day from a protocol defined intent-to-treat (ITT) analysis of the Femara and tamoxifen monotherapy arms in the Breast International Group (BIG) 1-98 study. Also included were results from an additional post-hoc censored analysis. The results were presented at the San Antonio Breast Cancer Symposium, an international symposium for scientists and clinicians in breast cancer.

Femara was indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer and treatment of early invasive breast cancer in postmenopausal women who had received prior standard adjuvant tamoxifen therapy. It could be used as first line treatment in postmenopausal women with advanced breast cancer. It was indicated for treatment of advanced breast cancer in postmenopausal women in whom tamoxifen or other anti-oestrogen therapy had failed and could be used as pre-operative therapy in some defined postmenopausal women to allow subsequent breast conserving surgery.

COMPLAINT

AstraZeneca noted that the press release, specifically tailored for the UK media, related to the latest results of a large international study comparing letrozole with tamoxifen in the treatment of early breast cancer which were released at a prestigious conference.

The title of the press release 'Femara (letrozole) FIRST aromatase inhibitor to indicate OVERALL SURVIVAL BENEFIT versus tamoxifen when taken for five years after breast cancer surgery' implied a significant survival benefit for letrozole over tamoxifen, which would be considered a major breakthrough in this field, worthy of significant press coverage. However, only upon further reading did it become evident that the title was in fact an exaggeration of a study result that failed to reach statistical significance (p=0.08). AstraZeneca alleged that the press release was therefore misleading in breach of Clause 22.2.

Novartis Oncology issued this press release via a web information distribution service. AstraZeneca noted that consumer journalists accessed this web information distribution service and the outputs were most likely to be read by the public. The press release raised unfounded hopes of successful treatment (an increase in survival), a claim that could not be substantiated by the current evidence in breach of Clause 22.2. Patients reading this information would be encouraged to demand letrozole over other aromatase inhibitors breaching Clause 22.2. There was no evidence of survival benefit for any of the aromatase inhibitors used in this setting.

The intention of the headline was to mislead readers into believing letrozole had achieved a survival benefit over tamoxifen. This was further evident by the quotation in the press release by a senior company spokesman, that 'The survival data shown may offer new promise for breast cancer patients'. All aromatase inhibitors had shown benefits in disease-free survival in the adjuvant setting. However there was no 'new promise' for these patients. Based on these data it would still be inappropriate for health professionals to counsel their patients on the 'promise' of a survival benefit from any aromatase inhibitor, letrozole included.

AstraZeneca was further concerned by the statement 'Long-term follow-up from major, independent BIG 1-98 trial adds further evidence that starting with Femara may be the optimal treatment strategy **versus tamoxifen**' (emphasis added). There was no new evidence from this analysis that suggested this was the case. Novartis had tried to use a non-significant survival benefit to suggest that letrozole was superior to anastrozole (AstraZeneca's product Arimidex), the only other licensed aromatase inhibitor in this setting. This was incorrect as neither had shown a statistically significant overall survival benefit in the adjuvant setting, and in any case this claim would only be appropriate in the context of a clinical trial directly comparing letrozole with other aromatase inhibitors. Patients reading this kind of information would be encouraged to demand letrozole over other aromatase inhibitors in breach of Clause 22.2.

AstraZeneca stated that the press release referred to a separate censored analysis, which was 'in favour' of letrozole, but did not clearly state that the analysis was not protocol defined and performed *post hoc* in a population that had been un-blinded, which severely limited the ability to assess the significance of the result. This was further evident in the slides from the presentation of the data which did not refer to event numbers, nor to a p value. The press release did not make clear any of the caveats of this analysis, further misleading readers as to the robustness of the data.

During inter-company dialogue Novartis suggested it qualified the statement by adding a non-significant p value to the press release. However companies could not expect consumer media to understand the subtleties of complex data and it could potentially mislead readers by misunderstanding press releases. There was further evidence that this press release had been taken out of context; a Daily Mail article clearly stated that letrozole reduced the risk of death by 20%, with no reference to the fact that the results were non-significant. The article would encourage patients to demand a specific aromatase inhibitor. A non-significant survival result did not justify providing information to the public in this manner and was in breach of Clause 22.2. Novartis had failed to maintain high standards, and press releases of this nature brought discredit to, and reduced confidence in, the pharmaceutical industry.

In summary AstraZeneca believed that this press release grossly misled health professionals and the public into believing that Femara had achieved a significant survival benefit over tamoxifen breaching Clauses 22.2, 9.1 and 2.

RESPONSE

Novartis stated that BIG 1-98 was an international, double-blind, controlled trial of postmenopausal women with hormone receptor positive early breast cancer (n=8,010). Patients were randomised to adjuvant treatment with either Femara for 5 years, tamoxifen for 5 years or a sequence of the two in either order. In summary -

- The study was independently led by the International Breast Cancer Study Group (IBCSG) with financial and monitoring support provided by Novartis.

- Two previous analyses of several endpoints, undertaken with median follow up of 26 and 51 months respectively, demonstrated that 5 years of Femara was superior to tamoxifen through assessment of several endpoints, most notably the primary endpoint of disease-free survival and time to distant recurrence (metastases). The first of these reports, in 2005, resulted in the approval of the indication, 'Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer'.

- The results also led IBCSG to take the ethical decision to un-blind the tamoxifen 5 year arm and offer those patients a choice of switching to Femara.

- ITT analysis presented at the conference included the 4,922 patients that were randomised to Femara or tamoxifen for 5 years. This was pre-specified in the protocol to occur when 10 years had elapsed since the start of randomisation in 1998. The median follow up for this analysis was 76 months.

- Following un-blinding in 2005, approximately a quarter (25.2%) of the patients originally randomised to tamoxifen selected to cross over to Femara. The median duration of treatment with Femara in these patients was 18 months. These patients remained in the tamoxifen arm for the ITT analysis and therefore, the ITT analysis included significant bias towards tamoxifen. Despite this bias, statistically significant differences favouring Femara were observed in the primary endpoint of disease-free survival and time to distant recurrence and a p value of 0.08 was observed for the secondary endpoint of overall survival.

- To estimate the impact of the selective crossover, IBCSG did a censored analysis of the ITT population. Data was censored from patients at the time of crossover. In this second analysis, a hazard ratio (HR) of 0.81 was observed for overall survival, representing a relative risk reduction of 19% for Femara versus tamoxifen. This was statistically significant, with the 95% confidence interval not crossing 1.00 (95% CI: 0.69 – 0.94).

Novartis submitted that pharmaceutical companies normally announced results from major clinical trials and the communication of these newsworthy results was in order to inform people in the UK who were interested in the treatment of breast cancer, including health professionals, the media and the public.

Clause 22.2 allowed such information to be made available via a press release to members of the public as long as this was factual and presented in a balanced way. Novartis believed that the press release presented the data from the reported analyses in a factual and balanced manner and objectively represented the IBCSG findings. Furthermore it did not believe that the results as presented raised unfounded hopes of successful treatment as alleged or would encourage members of the public to ask their health professionals to prescribe Femara.

Novartis noted that the full press release heading was:

Femara (letrozole) FIRST aromatase inhibitor to indicate OVERALL SURVIVAL BENEFIT versus tamoxifen when taken for five years after breast cancer surgery

- *Femara showed reduced risk of death by 13% (P=0.08) versus tamoxifen, despite inclusion of patients who had switched over from tamoxifen to Femara during the study period, following the study's unblinding*

- *In a separate censored analysis excluding patients after they crossed over to Femara, reduction in risk of death was 19% (HR= 0.81, 95% CI: 0.69-0.94)*

- *Long-term follow-up from major independent BIG 1-98 trial adds further evidence that starting with Femara may be the optimal treatment strategy versus tamoxifen.*

As described above, it was important to consider both analyses from the BIG 1-98 study presented at the December meeting. Both analyses were presented in the press release header and the explanatory text below and therefore faithfully represented the IBCSG presentation of the BIG 1-98 study update in a balanced way.

Novartis believed that the title was factually correct. The word 'indicate' clearly conveyed that overall superiority had not been proven and did not exaggerate the study results. This was further supported by bullet points immediately below the title which stated, together with corresponding statistical data, the trial results from two separate analyses presented at the meeting. The second paragraph of the main body of the press release specifically stated that the difference in overall survival in the ITT analysis was not statistically significant.

No indication of an overall survival benefit versus tamoxifen had previously been demonstrated in an adjuvant aromatase inhibitor trial. The Arimidex, Tamoxifen, Alone or in Combination trial in the adjuvant setting failed to demonstrate a significant benefit for anastrozole versus tamoxifen in terms of overall survival, despite 100 months' median follow up (HR, 0.97; 95% CI, 0.86-1.11; p=0.7); the first report from the Tamoxifen Exemestane Adjuvant Multinational trial was presented at the San Antonio Breast Cancer Symposium in December 2008 and no significant overall survival benefit for exemestane (Pfizer's product Aromasin) was demonstrated over tamoxifen. The use of the term 'first' was therefore justified in this context.

Novartis believed that the two analyses of overall survival in the BIG 1-98 study, which included 4,922 patients and was independently led by IBCSG was newsworthy for health professionals and others interested in the treatment of breast cancer.

Novartis also believed that because the results from this independent presentation at the prestigious meeting had been presented in a factual and balanced way, the press release did not mislead readers to draw inaccurate conclusions.

The press release did not include statements that encouraged members of the public to demand Femara over other treatments currently offered for the adjuvant treatment of hormone receptor positive early breast cancer. Novartis did not believe that the title of the press release was in breach of Clause 22.2 as alleged.

Novartis believed the press release to be relevant and of interest to consumer journalists and their readers. The information included in the IBCSG presentation of the BIG 1-98 study update substantiated a favourable benefit of Femara over tamoxifen and the results were faithfully and accurately presented in a balanced manner by the press release. No 'unfounded' hopes of successful treatment were given by the press release, in fact, it informed journalists of results from a large, international, independent clinical study that were important and significant to anyone interested in the treatment of early breast cancer.

AstraZeneca had included an article from the Daily Mail Online, which was published the day after the results were presented. As far as Novartis was aware, this was the only resulting article published in the national consumer press. Novartis noted that the article in the newspaper edition of the Daily Mail was a relatively small, quarter page article, published on page 28. Novartis believed that AstraZeneca had based its assertion that patients would be led to 'demanding' Femara on this one short article. The article reported the results from the study in a balanced way and then referred to aromatase inhibitors in general and placed their use in context against the use of tamoxifen. Therefore Novartis did not accept that the press release was in breach of Clause 22.2 based on the allegation that unfounded hopes of successful treatment would be raised and patients could be encouraged to ask their health professional to prescribe Femara.

Novartis noted the conclusions in the BIG 1-98 slide set: 'Updated results of BIG 1-98 suggest superior overall survival with letrozole compared with tamoxifen'. The quotation in question accurately

represented the conclusions that this data 'suggests' superiority of Femara over tamoxifen and that it 'may' offer new promise for a significant number of patients with breast cancer. A large proportion of women with early breast cancer who were appropriate for adjuvant endocrine treatment (eg tamoxifen, aromatase inhibitors), received tamoxifen.

The new evidence presented at the meeting confirmed previous results from the BIG 1-98 study with a median follow up of 76 months, which demonstrated through the analysis of several endpoints that Femara was superior to tamoxifen. This statement clearly referred to a comparison of Femara and tamoxifen with the words 'versus tamoxifen'. The comparator medicine, tamoxifen, in the BIG 1-98 trial was mentioned throughout the press release heading and in four paragraphs of the body of the press release text. No statement in the press release suggested that Femara was superior to anastrozole. As AstraZeneca correctly pointed out, there were no direct clinical comparisons of these two aromatase inhibitors in the adjuvant treatment setting. The press release would not encourage patients to demand Femara over other aromatase inhibitors and therefore, Novartis believed there was no breach of Clause 22.2.

The information relating to the censored analysis read:

> 'To explore the impact of the selective crossover, an additional analysis was conducted censoring follow-up times at the date of crossover to letrozole for 25% of the patients in the tamoxifen arm. In this analysis, a 19% reduction in risk of death (HR=0.81, 95% CI: 0.69-0.94) was observed in favour of Femara.'

This was an accurate and balanced representation of the facts released by the IBCSG at the meeting. The language expressly indicated that this was an extra analysis to explore the impact of selective crossover in the ITT analysis results. It was clearly stated that the censored analysis was performed as 'an additional analysis' to the protocol-defined ITT analysis described in the preceding paragraph. Due to the un-blinding and subsequent unplanned, selective crossover to Femara in the ITT analysis, it was important to consider both analyses in context to better estimate the effect of Femara versus tamoxifen if the trial had remained fully blinded. The press release had presented these data in a factual and balanced manner, and there was no attempt to mislead readers as alleged.

In summary, Novartis believed that the press release presented the data in a factual and balanced way. The title was not an unqualified claim for superiority but highlighted that the data indicated that an improvement was seen versus tamoxifen over 5 years. The press release was clear throughout that the data reported was versus tamoxifen. It did not raise unfounded hopes of successful treatment or contain statements which would encourage members of the public to ask their health professional to prescribe a specific prescription only medicine. Therefore Novartis did not believe that the press release warranted breaches of Clause 22.2 nor that it had failed to maintain high standards or brought discredit to, or reduced confidence in, the pharmaceutical industry warranting breaches of Clauses 9.1 or 2.

PANEL RULING

The Panel noted the results from the new data. The reduced risk of death for Femara versus tamoxifen was not statistically significant (p= 0.08) in the ITT analysis. The Panel considered that the heading to the press release that Femara was the '… FIRST aromatase inhibitor to indicate OVERALL SURVIVAL BENEFIT versus tamoxifen… ' was not a fair reflection of the study results. The Panel considered that the heading gave the clear impression that a clinically significant difference had been established between the products which was not so. The difference was not statistically significant. The Panel did not consider that the use of the word 'indicate' negated the otherwise misleading impression as submitted by Novartis. The Panel considered that the heading was misleading as alleged and a breach of Clause 22.2 was ruled.

The Panel considered that the press release raised unfounded hopes of successful treatment and would in effect encourage patients to ask for a specific prescription only medicine, Femara, as alleged. A breach of Clause 22.2 was ruled.

With regard to the claim 'Long-term follow-up from major independent BIG 1-98 trial adds further evidence that starting with Femara may be the optimal treatment strategy versus tamoxifen' the Panel noted that there were no clinical studies comparing Femara and anastrozole. There were treatment strategies other than Femara. The Panel considered that the press release did not make this sufficiently clear. In the Panel's view the use of the phrase 'may be' did not negate the impression that Femara was the optimal treatment strategy versus tamoxifen. The Panel considered that patients would be inclined to ask for Femara in preference to other aromatase inhibitors. The Panel considered that the claim in question was misleading in this regard and a breach of Clause 22.2 was ruled.

The statement 'To explore the impact of the selective crossover, an additional analysis was conducted censoring follow-up times at the date of crossover to letrozole for 25% of the patients in the tamoxifen arm. In this analysis a 19% reduction in risk of death (HR 0.81, 95% CI: 0.69-0.94) was observed in favour of Femara' did not in the Panel's view reflect the nature of the data. This analysis was not protocol defined and was performed *post-hoc* with the tamoxifen arm un-blinded. The Panel did not accept Novartis' submission that it was clear that the analysis was additional to the ITT analysis. The Panel

considered the statement was misleading as insufficient detail was provided about the nature of the data. A breach of Clause 22.2 was ruled.

In the Panel's view the Daily Mail article provided by AstraZeneca to support its complaint demonstrated that the press release was misleading.

The Panel did not consider that it was a breach of the Code *per se* to issue a press release about non-significant survival results and on this narrow point no breach of Clause 22.2 was ruled.

The Panel was concerned that a misleading press release had been issued about data that would be of great interest to the public and health professionals. High standards had not been maintained and a breach of Clause 9.1 was ruled.

With regard to the alleged breach of Clause 2 the Panel considered it was very important that press releases, particularly those that were made available to consumer journalists about sensitive issues such as survival in cancer patients, were fair, factual and not misleading. Clause 2 was used as a sign of particular censure and reserved for such use. The Panel considered that the circumstances warranted such a ruling and a breach of Clause 2 was ruled.

Complaint received **20 January 2009**

Case completed **24 February 2009**

CASE AUTH/2202/1/09

LILLY v NOVO NORDISK

Diabetes supplement in The Times

Lilly alleged that an article 'Gut protein drug expected to help improve control' within a diabetes supplement distributed with The Times newspaper, constituted pre-licence promotion of liraglutide in breach of the Code. The article, based upon an interview with a senior executive of Novo Nordisk, referred to clinical trials of liraglutide which had demonstrated 'better blood glucose control …' and that it '… has also helped people reduce weight'.

Lilly did not consider that the supplement, which had been sponsored by Novo Nordisk and distributed to coincide with World Diabetes Day, was a reasonable forum to 'discuss future [unlicensed] therapies' as had been asserted by Novo Nordisk in inter-company dialogue.

The detailed response from Novo Nordisk is given below.

The Panel noted that the supplement at issue had been fully funded by Novo Nordisk which had full editorial control, owned the copyright and was part of the editorial team.

The article, 'Gut protein drug expected to help improve control' was the record of an interview by a journalist with Novo Nordisk's chief science officer. The Panel considered that the inclusion of this article showed that Novo Nordisk had contributed material about liraglutide and so in that regard had been able to influence the content of the supplement in a manner which favoured its interests. There was no strictly arm's length arrangement between the provision of sponsorship and the content of the supplement. The Panel thus considered that Novo Nordisk was responsible for the content of the supplement in relation to compliance with the Code.

In his interview, Novo Nordisk's chief science officer stated, *inter alia*, that clinical trials of liraglutide had shown that not only did people maintain better control of their blood glucose levels but that it also helped them to lose weight. The Panel did not accept that the supplement in The Times was an acceptable forum to publish the results of clinical trials as submitted by Novo Nordisk. The Panel considered that patients would read the article and see liraglutide, with its 'single daily injection' and 'better glucose control' as a possible improvement on their current therapy and thus be encouraged to ask their health professional to prescribe it. In this regard the Panel considered it irrelevant that the product was as yet unavailable to prescribe. A breach of the Code was ruled. The Panel further considered that the article promoted liraglutide to the public prior to the grant of a marketing authorization. High standards had not been maintained. Breaches of the Code were ruled.

The Panel considered that companies should take particular care when producing materials for the public. The Panel considered that in this regard Novo Nordisk had failed to exercise due diligence and thus brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

Eli Lilly and Company Limited alleged that an article in a 16 page diabetes supplement, 'Changing the Future of Diabetes', which was distributed with The Times on 14 November, promoted Novo Nordisk Limited's product liraglutide prior to the grant of its marketing authorization. Inter-company dialogue had failed to resolve the matter.

COMPLAINT

Lilly alleged that the article, 'Gut protein drug expected to help improve control' constituted the pre-licence promotion of liraglutide to health professionals and the public and breached the Code.

On 14 November 2008 The Times newspaper and a media agency, in association with Novo Nordisk and other stakeholders, published the supplement entitled 'Changing the Future of Diabetes'. The article on page fourteen, 'Gut protein drug expected to help improve control' was based upon an interview with Novo Nordisk's chief science officer. The chief science officer explained the developmental hypothesis and putative mode of action of liraglutide, that its use involved a single daily injection and claimed that 'Clinical trials of liraglutide, have shown that people have better blood glucose control…'. The article also elaborated on the observation that liraglutide '… has also helped people reduce weight'. The article mentioned that liraglutide was currently unapproved in Europe and America; a fact corroborated by Novo Nordisk.

Further, in its response to Lilly's concerns, Novo Nordisk clearly acknowledged that the publication date for these pre-licence discussions of liraglutide was intended to coincide to 'mark World Diabetes Day' and 'to raise awareness of a wide variety of developments in the treatment of diabetes'. The latter was also evident in the interview with the managing director of Novo Nordisk UK & Ireland as reported on page three of the supplement. It was clear that Novo Nordisk was commercially motivated to use the opportunity afforded by the wide circulation of the supplement and the heightened awareness of diabetes, occasioned by a high-profile event such as

World Diabetes Day, to promote liraglutide. Indeed, Novo Nordisk had acknowledged that these pre-licence discussions were undertaken to disseminate information about Novo Nordisk products in development given the 'significant public and financial interests' in these.

Lilly did not accept the assertion that a publication sponsored by Novo Nordisk in The Times supplement was a reasonable forum to 'discuss future [unlicensed] therapies'. Given the latter, this was clearly a promotional publication, irrespective of the fallacious rationale proffered by Novo Nordisk regarding the 'context' in which the information regarding liraglutide appeared.

Lilly disagreed with Novo Nordisk's assertion that the provision of pre-licence information regarding liraglutide, to consumer journalists and its subsequent publication in consumer media constituted an educational activity. Equally concerning was the suggestion that the provision of information about liraglutide constituted 'raising awareness of the disease [diabetes]'. In this regard Lilly invited the Authority to consider that this activity was also in breach of the Medicines and Healthcare products Regulatory Agency (MHRA) Guidelines for Conducting Disease Awareness Campaigns.

Lilly was also concerned that Novo Nordisk appeared to rationalise its arguments in support of this pre-licence activity on the premise that Clauses 22.1 and 22.2 could not be applied to liraglutide 'as it cannot be prescribed', the premise for the latter being that 'liraglutide has not yet received a licence, [and therefore] it cannot be defined as a prescription only medicine'.

Lilly believed that the publication constituted the pre-licence promotion of liraglutide to the public, in breach of Clauses 9.1, 3.1, 22.1 and 22.2. Due to the serious nature of this matter and the obvious failing of Novo Nordisk to appreciate some of the most fundamental tenets of the Code, as evidenced by its response to Lilly of 4 December, Lilly also invited consideration of a breach of Clause 2.

RESPONSE

Novo Nordisk noted that the supplement contained a wide variety of articles, not specifically focusing on treatments or new drug development. As such, Novo Nordisk believed the publication of the article to coincide with World Diabetes Day, which was an International Diabetes Federation initiative to highlight diabetes, and was what the article was in support of, was valid and relevant, since the general impression of the publication was of raising the awareness of the disease, rather than specific company or product promotion. Novo Nordisk noted that Lilly had also referred to the interview with its managing director on page three of the supplement. However, Novo Nordisk understood that this section of the supplement did not constitute part of the complaint, and Novo Nordisk could not see any part of this section which corroborated the original complaint.

Novo Nordisk firmly believed that the supplement was an example of raising the profile of diabetes supported by Novo Nordisk amongst other stakeholders. With this in mind, Novo Nordisk believed the provision of information regarding clinical research (specifically, in the article in question, regarding liraglutide), complied with Clause 22. The article quite clearly stated that liraglutide '…is currently lodged with the relevant authorities in Europe and America' therefore positioning it as a future development rather than a current product that could be prescribed.

In addition to this, it was made very clear throughout the article that the stated effects of liraglutide were found as a result of clinical trials, and therefore Novo Nordisk considered the article constituted research findings. Indeed, Lilly had quoted from the article 'Clinical trials of liraglutide have shown that people have better blood glucose control'. The other quotation in this paragraph; '…has also helped people to reduce weight' should be taken in context, as the start of that particular sentence was 'In published clinical trials…'.

The argument raised by Lilly that this article was in breach of the MHRA Guidelines for Conducting Disease Awareness Campaigns depended on the view that the article made product-specific promotional claims. As Novo Nordisk had outlined above, it firmly believed that the mention of clinical research findings of a drug such as liraglutide was of interest, particularly when taken in context with other new and future developments also covered in the supplement.

In summary, Novo Nordisk considered that the article was a valid outline of the clinical research findings of liraglutide. The fact that the effects of the medicine related to clinical research was made very clear throughout the article, as was the fact that it was not yet approved. With this in mind, Novo Nordisk considered that it had complied with the Code and that it had not breached Clauses 9.1, 3.1, 22.1 22.2 or Clause 2.

Furthermore Novo Nordisk was committed to raising awareness of diabetes not only in the UK but also across the world. With more than 80 years' supporting diabetes Novo Nordisk spent off [sic] effort in this non product, non-promotional supplement where it, together with many diabetes stakeholders including patient organisations and health professionals, raised the awareness of diabetes and the importance of improving the treatment of diabetes, which was an example of one of Novo Nordisk's key values in line with its corporate social responsibility.

In response to a request for further information Novo Nordisk submitted that, for the third successive year, it, in association with its partners, sponsored the supplement which was published in The Times on World Diabetes Day. The main objective of the

supplement, as in previous years, was to inform, educate and promote diabetes care and management. In addition, it provided an opportunity for Novo Nordisk and its partners to communicate to all their relevant audiences how individually and collectively they were helping society tackle diabetes.

The media agency that managed the production of the supplement had a contract with The Times to distribute educational supplements with the paper. In the case of 'Changing the Future of Diabetes', the supplement was instigated by the agency and fully funded by Novo Nordisk. A copy of the sponsorship agreement between Novo Nordisk and the agency, dated 18 August 2008 was provided.

The supplement was written by a Times freelance journalist, and the review process was by committee between Novo Nordisk and all partners who contributed content. Novo Nordisk provided a list of co-sponsors. The authors were contacted directly by the journalist and Novo Nordisk checked the output for scientific accuracy for the Novo Nordisk contributors.

In addition to distribution with The Times on 14 November 2008, the clinical research group distributed approximately 80 copies on World Diabetes Day only; no copies were distributed by the sales and marketing teams. There were no plans for further dissemination.

PANEL RULING

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes. In the case of sponsored material aimed at the public consideration would also have to be given to the requirements of Clause 22.

The Panel noted that Clause 22.1 prohibited the advertising of prescription only medicines to the public. Clause 22.2 permitted information to be supplied directly or indirectly to the 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.

The supplement at issue had been fully funded by Novo Nordisk and was published to coincide with World Diabetes Day. The order confirmation between Novo Nordisk and the media agency that managed the publication of the supplement stated that Novo Nordisk had placed an order for sponsorship of the supplement. It further showed that Novo Nordisk had full editorial control, owned the copyright and was part of the editorial team. It appeared that the company had ordered 5,000 copies of the supplement; Novo Nordisk's clinical research group had distributed 80 copies on World Diabetes Day. The copy deadline was given as 31 October.

The article at issue, 'Gut protein drug expected to help improve control' was the record of an interview by a journalist with Novo Nordisk's chief science officer. The Panel considered that the inclusion of this article showed that Novo Nordisk had contributed material about liraglutide and so in that regard had been able to influence the content of the supplement in a manner which favoured its interests. There was no strictly arm's length arrangement between the provision of sponsorship and the content of the supplement. The Panel thus considered that Novo Nordisk was responsible for the content of the supplement in relation to compliance with the Code.

In his interview, Novo Nordisk's chief science officer referred to liraglutide stating that clinical trials of the product had shown that not only did people maintain better control of their blood glucose levels but that it also helped them to lose weight. The article stated that the medicine was currently lodged with the relevant authorities in Europe and the US and, if approved, would be expected to be available from mid 2009. The Panel did not accept that the supplement in The Times was an acceptable forum to publish the results of clinical trials as submitted by Novo Nordisk. The Panel considered that patients would read the article and see liraglutide, with its 'single daily injection' and 'better glucose control' as a possible improvement on their current therapy and thus be encouraged to ask their health professional to prescribe it. In this regard the Panel considered it irrelevant that the product was as yet unavailable to prescribe. A breach of Clause 22.2 was ruled. The Panel further considered that the article promoted liraglutide to the public. A breach of Clause 22.1 was ruled. Further, the product had, in effect, been promoted prior to the grant of a marketing authorization. A breach of Clause 3.1 was ruled. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel considered that companies should take particular care when producing materials for the public. The Panel considered that in this regard Novo Nordisk had failed to exercise due diligence and thus brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received **23 January 2009**

Case completed **10 March 2009**

CASE AUTH/2203/1/09

JOHNSON & JOHNSON v PFIZER

Champix journal advertisement

Johnson & Johnson alleged that the claim 'CHAMPIX [varenicline] at 12 weeks provides significantly greater quit success vs. NRT [nicotine replacement therapy] (NiQuitin CQ clear)' in a journal advertisement issued by Pfizer was misleading and not supported by robust data. The study from which the claim was derived was an open-label comparison of Champix tablets and NRT patches and almost half of the subjects had previously, unsuccessfully, used NRT patches to quit smoking. The significant biases in the study could have easily been overcome by using a double-dummy design and excluding patients who had previously used NRT. The study was not a fair comparison and should not be used to substantiate a superiority claim for Champix vs NRT.

The detailed response from Pfizer is given below.

The Panel noted that the study from which the claim was derived was an open-label, randomised comparison of a 12 week standard regimen of Champix with a 10 week standard regimen of NRT for smoking cessation. All patients were motivated to quit and had not used any form of NRT in the previous 6 months. The Panel noted each party's submission about the study methodology and limitations. The study authors noted that a limitation was its open-label design and a detailed discussion of the study's limitations appeared in the published paper.

The Panel noted that whilst an open-label design would not necessarily preclude the use of study data in promotional material, readers had to be provided with sufficient information to enable them to assess the data. The Panel noted the study authors' conclusions that 'motivational influences are likely to exist in a real-world setting and the outcomes of this study show that varenicline is more effective than transdermal nicotine in enhancing quit rates in *an open-label setting*' (emphasis added). The Panel did not consider that the claim at issue was a fair reflection of the study findings in this regard. The main body of the advertisement gave no relevant details about the study design and so the reader would be unaware of the basis of the data. The Panel considered the claim 'Champix at 12 weeks provides significant greater quit success vs NRT (NiQuitin CQ Clear)' was misleading in this regard and a breach of the Code was ruled.

Johnson & Johnson Limited complained about a Champix (varenicline) advertisement (ref CHA432a) issued by Pfizer Limited and published in GP, 11 April 2008.

COMPLAINT

Johnson & Johnson alleged that the claim 'CHAMPIX at 12 weeks provides significantly greater quit success vs. NRT [nicotine replacement therapy] (NiQuitin CQ clear)' was misleading and not supported by robust data. This claim should not be referenced to Gonzales *et al* (2006) but to Aubin *et al* (2008). Pfizer had agreed that future advertising would reference this study correctly.

Aubin *et al* (2008) used an open-label design which immediately introduced a significant level of bias. The International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline on Statistical Principles for Clinical Trials clearly stated in section 2.3 Design Techniques to Avoid Bias: 'The most important design techniques for avoiding bias in clinical trials are blinding and randomisation…'.

The ICH guidelines referred to the following points:

- Along with randomisation, blinding was one of the two most important techniques to avoid bias in clinical trials, and therefore ensure a fair comparison between two treatments
- Blinding should be considered a normal feature in clinical trials
- 'Extensive efforts' should be made to overcome any difficulties in achieving blinding – if two treatments were clearly different a double-dummy technique should be used
- If a double-blind design was not possible, then single blinding should be considered.

Any non-blinded study had serious limitations, and interpretation of results from non-blinded studies should be made very carefully and with these limitations in mind. It was difficult to envisage a scenario in which a clear statement claiming superiority of one treatment over another could ever be justifiably supported solely from a non-blinded study. A non-blinded study inevitably introduced bias which applied to both subjects and investigators and this bias could extend to selection, motivation, measurement and analysis.

Expectations were likely to be much higher for any new product and the fact that patients in the Champix group knew they had been allocated a novel smoking cessation treatment significantly biased the study outcome in favour of Champix. In two of Pfizer's pivotal studies comparing Champix and bupropion (Jorenby *et al* 2006 and Gonzales *et al*), varenicline demonstrated abstinence rates of around 44% for the same time point used in Aubin *et al* (last four weeks of treatment). Despite similarities between the studies in terms of the level

of intervention and the demographics of the smokers, these abstinence rates were considerably lower than the 55% observed by Aubin *et al*. This suggested that knowledge of treatment in patients receiving Champix resulted in greater motivation to quit than those receiving NRT. As motivation to quit was a key factor in the likelihood of a successful quit attempt, this was likely to have biased the results in favour of Champix.

The fact that three patients randomised to NRT refused such treatment clearly suggested there would be a motivational bias in favour of Champix. Moreover, it appeared likely that some patients might have only participated in this study to receive varenicline. The authors stated that 'a refusal to participate further was less likely with varenicline than with NRT. A double blind design may have avoided such biases'. The authors further acknowledged that 'the differential dropout rate after medication assignment and before the first dose of treatment suggests that some motivational bias may have influenced the results'.

Johnson & Johnson disagreed with Pfizer's claim that it was acceptable to use this open-label study as the basis for strong comparative claims against NRT products. This study was open to a number of critically important biases and the Code required that all claims were supported by the appropriate evidence. In the case of comparative claims, it was particularly important that appropriately robust studies demonstrated that one treatment was more effective than another.

Aubin *et al* accepted the limitations of an open-label design, noting that a double-dummy design would have enabled the study to be appropriately blinded. They stated that a double-dummy design was not possible as 'technical problems made it difficult to create NRT and placebo patches that were indistinguishable from one another in appearance and odour'. This was very difficult to understand as nicotine was colourless and odourless and when the study was performed Pfizer manufactured and marketed a range of NRT products, including NRT patches, and had sponsored a number of placebo-controlled studies which included a placebo NRT patch. The obvious conclusion was that 'extensive efforts' were not made to overcome difficulties in achieving blinding.

In addition to the contention that a properly blinded study was not possible, Pfizer also argued that an open-label design was appropriate because it reflected the 'real world' situation. Johnson & Johnson did not accept this as a valid argument; it was clearly at odds with the guidance given in the ICH Harmonised Tripartite Guideline on Statistical Principles for Clinical Trials. A clinical trial should be a controlled experiment and variables other than those being investigated (in this case medical treatment) should be eliminated where possible. The purpose of a controlled clinical trial was not to represent the real world situation but rather to detect genuine differences between two treatments in a controlled setting. Unless a clinical trial had been designed to eliminate the biases which existed in the real world, fair conclusions about the comparative efficacy of two treatments could not be made. If the intention of the study had been to examine the real world scenario, then randomisation was not appropriate, and patients should have been able to select treatment. In this scenario, an audit rather than clinical trial would have been more appropriate.

As regards the applicability of the trial to the real world, the authors suggested that motivational influences were likely to exist in the real world. This might be the case. However, this did not negate the fact that the study was not designed to examine the real world. In addition, motivation within the real world would change over time as some smokers would inevitably fail to quit with varenicline. Hence, in the real world, the expected improved motivation with varenicline was likely to be the highest when the product was first introduced and would reduce over time. The authors cited the open-label design of the study as a key limitation.

Pfizer submitted that Aubin *et al* was included in the Cochrane Systematic review on varenicline, and noted that the reviewers stated: 'One open-label trial of varenicline versus nicotine replacement therapy demonstrated a modest benefit of varenicline over NRT with a RR at week 52 of 1.31 (95% CI 1.01 to 1.71)'. However, Pfizer failed to mention that the reviewers also stated 'Aubin 2008 was an unblinded open-label trial, which may have led to the differential drop-out rates after randomization, with nine participants assigned to nicotine patch declining to take part compared with two in the varenicline group'. Hence the Cochrane review acknowledged potential bias within the trial.

A further limitation of the study which introduced significant bias was the fact that almost half the subjects (46.2% in the NRT group) had previously used NRT patches in a quit attempt. The fact that when enrolled into the study, all subjects smoked at least 15 cigarettes per day meant that any of them who had previously used NRT patches in a quit attempt had been unsuccessful, as they had relapsed. Johnson & Johnson believed this represented a significant source of bias for a number of reasons and was compounded by the use of an open-label design.

Firstly, it was well accepted that some patients, for instance those who were more highly dependent, or those who had failed to quit with single NRT therapy, might benefit from higher doses of nicotine. This was why the National Institute for Health and Clinical Excellence (NICE) and Action on Smoking and Health (ASH) recommended use of combination NRT therapy (a patch plus an acute format) in some smokers. Hence, by including smokers who had failed to quit previously using NRT, this study might have included a large number of recalcitrant smokers who required higher dose NRT treatment.

Secondly, as described previously, it was widely accepted that motivation to quit was important in treatment success. Therefore, with full knowledge of their treatment allocation and an awareness that they had previously used NRT patches unsuccessfully, almost half the subjects in the NRT group were likely to have had much lower expectations of treatment success and lower motivation to quit. Taking these factors into consideration, it was very likely that the inclusion of a significant number of patients in the NRT group who had previously failed on their allocated treatment resulted in a lower overall quit rate in that group. Again, this would significantly and unfairly bias the study outcome in favour of Champix.

This difference in motivation was likely to be responsible for the differential drop out rates following randomisation of patients to the two treatment arms. Aubin *et al* and the Cochrane Collaborative acknowledged the difference in drop out rates between the groups. Furthermore, the authors clearly stated 'The differential drop out rate after medication assignment and before the first dose of treatment suggests that some motivational bias may have influenced the results'. Therefore, it seems likely that differences in motivation would have biased the results in favour of varenicline.

In Jorenby *et al* and Gonzales *et al*, patients who had previously been exposed to bupropion were excluded in order to minimalise potential negative bias towards bupropion. Pfizer argued that subjects who had previously been treated with bupropion were excluded in these studies because of evidence suggesting that re-treatment with bupropion reduced efficacy. In support of this, Pfizer also quoted Gonzales *et al* (2001).

Gonzales *et al* (2001) did not assess the effect of previous treatment with bupropion on the efficacy of varenicline and in any case the authors concluded that bupropion was effective for re-treatment of smokers, regardless of previous smoking medication used. The authors however stressed that 'An understanding of the impact of these previous attempts to quit is vital for selecting medications that may be more successful in a future attempt to quit'. In this context, and given that prior use of bupropion was an exclusion criteria in Pfizer's pivotal studies of Champix, it was clearly inappropriate to include subjects who had previously relapsed following NRT therapy in a study comparing the efficacy of Champix with NRT. Interestingly, Gonzales *et al* (2001) stated that re-treatment with NRT of smokers who had previously used NRT had been only somewhat successful. In the absence of data, it was not safe to assume that previous treatment had no effect on subsequent treatment, and it was difficult to understand why patients who had relapsed following NRT were included in the study.

Johnson & Johnson noted that Jorenby *et al* and Gonzales *et al*, comparing varenicline and bupropion, were both double-blind.

Finally, Aubin *et al* conceded that the difference between the groups in treatment duration introduced yet another source of bias. It was likely that subjects in the varenicline group receiving a 12-week course of treatment would have better expectations and motivation than subjects in the NRT group who received a 10-week course of treatment.

In conclusion, Aubin *et al* was of very poor methodological quality and introduced a number of significant biases which could easily have been overcome by implementing a double-dummy design and excluding patients who had previously used NRT. This trial could not possibly be held up as a fair comparison of Champix and NRT and should not be used to substantiate a superiority claim for the efficacy of Champix over NRT.

The use of this claim was in breach of Clause 7.2 of the Code as it provided an unfair comparison without adequate supporting data.

RESPONSE

Pfizer stated that although the advertisement was no longer in use it was important to respond to the general critique of Aubin *et al*. Aubin *et al* was used in the Champix sales aid where Pfizer described the study design. Pfizer's presentation of Aubin *et al* in the sales aid was reviewed in a previous case, Case AUTH/2142/7/08, and was found not to be in breach of Clause 7.2.

Pfizer believed the design of Aubin *et al* was robust, and therefore it was appropriate to use the results in promotional materials. Pfizer did not agree that the claim 'Champix at 12 weeks provides significantly greater quit success vs NRT (NiQuitin CQ Clear)' was in breach of Clause 7.2.

Aubin *et al* was published online in Thorax, an international peer-reviewed journal. As detailed in the advertisement, the results showed that varenicline at 12 weeks provided significantly greater quit success compared with NiQuitin CQ Clear patch. This claim was supported by data from the study, which showed that the primary endpoint, continuous abstinence rate at end of treatment, was significantly greater for varenicline (55.9%) than NiQuitin CQ Clear (43.2%) ($p<0.001$, odds ratio 1.70, 95% confidence interval 1.26 to 2.28 as also included in the advertisement).

The authors concluded that 'The outcomes of this trial established that abstinence from smoking was greater and craving, withdrawal symptoms and smoking satisfaction were less, at the end of treatment with varenicline than with transdermal NRT'.

Aubin *et al* was a randomized, open-label clinical trial. Smokers had often made multiple failed quit attempts, including using various forms of NRT. As discussed by the authors, this population might

demonstrate a motivation towards trying an alternate therapy. Given the immense difficulty faced by this population in giving up smoking, it was an important question to ask whether varenicline, even with this motivation, could offer significantly greater quit rates compared with NRT at the end of treatment.

Pfizer submitted that blinding would have been technically difficult in this population. The authors stated that 'technical problems made it difficult to create NRT and placebo patches that were indistinguishable from one another in appearance and odour'. Before entering this trial, almost half of the patients had already tried to quit smoking with a nicotine patch. This fact presented technical difficulties to the study designers, who assumed that any difference between the therapeutic nicotine patch and the placebo patch would be detected. Skin irritation caused by nicotine in the therapeutic patch could not be duplicated in a placebo patch, for example – nor could the distinctive smell of the therapeutic patch.

Almost half the subjects (46.2% in the NRT group) had previously tried to quit and failed using a transdermal nicotine patch and in Johnson & Johnson's view this might have favoured varenicline. However, patients were excluded if they had used NRT within the previous 6 months. In addition, treatment by baseline covariate analysis demonstrated that there was no interaction ($p > 0.10$) with prior quit attempt using NRT or transdermal patch, suggesting that this did not influence the efficacy.

Johnson & Johnson raised the issue of the use of combination NRT therapy. Aubin *et al* was designed to address the efficacy of varenicline in comparison with a single form of NRT, it would require a separate study to assess efficacy of varenicline in comparison with combination therapy. The claim used in the advertisement clearly indicated that the results were comparing varenicline with a single form of NRT 'vs NRT (NiQuitin CQ Clear)'.

The study was included in the recently updated Cochrane review published online in 'Nicotine receptor partial agonists for smoking cessation' on 16 July 2008. The authors included the Aubin *et al* data in their review and in their results they stated that 'One open-label trial of varenicline versus nicotine replacement therapy demonstrated a modest benefit of varenicline over NRT with a RR at week 52 of 1.31 (95%CI 1.01 to 1.71)'. The Cochrane reviewers also stated that 'Aubin 2008 was an unblinded open-label trial, which may have led to the differential drop-out rates after randomisation, with nine participants assigned to nicotine patch declining to take part compared with two in the varenicline group'. It should be noted that the primary analysis population for the study was all randomized and treated, so the data set used to calculate the primary endpoint in Aubin *et al* used the population following the drop out of nine in the nicotine patch group and two in the varenicline group.

Within Aubin *et al* the analysis of the all randomized population was also included. The continuous abstinence rate at the end of treatment was significantly greater for varenicline (55.6%) than NiQuitin CQ Clear (42.2%), odds ratio 1.76 $p<0.001$. When comparing these results to those of the primary analysis population (all randomized and treated) the odds ratio for the all randomized and treated population (1.70) was numerically less favourable for varenicline than if the odds ratio all randomized population had been used (1.76). In order to address the possible bias from differential drop outs following randomization the authors prespecified in the study design that they would use the all randomized and treated population as the primary analysis population.

The NRT course of treatment finished 1 week earlier than the varenicline course of treatment and this in Johnson & Johnson's view might have favoured varenicline. The duration of therapy was as defined in the respective summaries of product characteristics (SPCs) for the products. To explore this further a prespecified sensitivity analysis compared, like for like, 4 week continuous rates for weeks 9–12 in both treatment groups and weeks 8–11 in both treatment groups and found that the overall conclusions remained unchanged.

Johnson & Johnson stated this study might have selected a population resistant to NRT, thereby favouring varenicline. Pfizer was not aware of any literature regarding the development of NRT resistance in people previously exposed to NRT. Two studies that compared varenicline with buproprion were also discussed which excluded patients who had previously been exposed to buproprion. The reason for this exclusion was because there was evidence that efficacy was reduced in individuals with prior exposure to bupropion compared with those who were bupropion naïve. The purpose of including Gonzales *et al* (2001) was to demonstrate the rationale for excluding patients who had previously been exposed to buproprion in the design of Jorenby *et al* and Gonzales (2006) *et al*; not to make any assessment about the effect of previous treatment with bupropion on the efficacy of varenicline as stated by Johnson & Johnson.

With the above in mind, Pfizer did not agree that this study should not be used to support comparisons between Champix and NRT.

PANEL RULING

The Panel noted that the title of the advertisement was 'The power to help them quit' which appeared above a visual of a cigarette splitting in half. The statement 'Now with direct NRT comparison' introduced three bullet points starting with the claim at issue 'Champix at 12 weeks provides significantly greater quit success vs. NRT (NiQuitin CQ Clear)'. The second bullet point read '1.7x greater odds of quitting smoking after Champix at 12 weeks vs. NRT

patch (odds ratio = 1.70; p<0.001)'. The first two bullet points were referenced in error to Gonzales *et al* (2006) instead of Aubin *et al*. The third bullet point read 'Champix also enables significantly more smokers to quit at 12 weeks than those who used bupropion or placebo' and was referenced to Gonzales *et al* 2006 and Jorenby *et al*. A footnote, asterisked to the second bullet point, explained that the recommended treatment course for Champix was 12 weeks and for NRT patch (NiQuitin CQ Clear) was 10 weeks. Continuous abstinence rate was [carbon monoxide] – confirmed at weeks 9-12 for Champix and at weeks 8-11 for NRT. No further details about Aubin *et al* were given.

The Panel noted that Pfizer referred to a previous case, Case AUTH/2142/7/08, wherein a comparison of the difference in quit success between Champix and NiQuitin at 12 weeks and 52 weeks, referenced to Aubin *et al*, was ruled not in breach of Clause 7.2. The Panel noted that the allegation currently before the Panel was not considered in Case AUTH/2142/7/08. The material at issue was also different.

The Panel noted that Aubin *et al* was an open-label, randomised trial to compare a 12 week standard regimen of Champix with a 10 week standard regimen of NRT for smoking cessation. All patients were motivated to quit and had not used any form of NRT in the previous 6 months. The study authors referred to the intent to treat analysis as a gold standard and explained that they reported the primary analysis population (those who were randomised and took at least one dose of medicine) in the efficacy results as this was the study's prespecified primary analysis population. The authors noted that this might underestimate the efficacy of Champix relative to NRT because of differential drop out after medication assignment.

The Panel noted each party's submission about the study methodology and limitations. The study authors noted that a limitation of the study was its open-label design and a detailed discussion of the study's limitations appeared in the published paper. The Panel noted the study authors' comment that technical problems made it difficult to create NRT and placebo patches that were indistinguishable in appearance and odour.

The Panel noted that whilst an open-label design would not necessarily preclude the use of data derived from Aubin *et al* in promotional material, readers had to be provided with sufficient information about the study to enable them to assess the data. The Panel noted the study authors' conclusions that 'motivational influences are likely to exist in a real-world setting and the outcomes of this study show that varenicline is more effective than transdermal nicotine in enhancing quit rates in **an open-label setting**' (emphasis added). The Panel did not consider that the claim at issue was a fair reflection of the study findings in this regard. The main body of the advertisement gave no relevant details about the study design and so the reader would be unaware of the basis of the data. The Panel considered the claim 'Champix at 12 weeks provides significant greater quit success vs NRT (NiQuitin CQ Clear)' was misleading in this regard and a breach of Clause 7.2 was ruled.

Complaint received **27 January 2009**

Case completed **5 March 2009**

CASE AUTH/2204/1/09

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY v ASTRAZENECA

Zoladex journal advertisement

The Medicines and Healthcare products Regulatory Agency (MHRA) alleged that a journal advertisement for Zoladex (goserelin), issued by AstraZeneca, was in breach of the Code because it included a reference to the MHRA. The advertisement, which gave AstraZeneca's perspective on a recent review of the class of medicines to which goserelin belonged, stated:

> **'The Medicines and Healthcare products Regulatory Agency (MHRA) recently reviewed the licence for goserelin 3.6 mg and 10.8 mg and updated the Summary of Product Characteristics (SmPC) to reflect these survival benefits. As such Section 5.1 of the goserelin SmPC details a wealth of survival data relating specifically to randomised controlled trials with goserelin.'**

The detailed response from AstraZeneca is given below.

The Panel noted that the Code prohibited reference in promotional material to, *inter alia*, the MHRA. The only exemption to this prohibition was if such reference was specifically required by the licensing authority. The MHRA had not specifically required AstraZeneca to include such a reference in its promotional material. The Panel therefore ruled a breach of the Code as acknowledged by AstraZeneca.

The Medicines and Healthcare products Regulatory Agency (MHRA) complained about a Zoladex (goserelin) advertisement (ref AZ-CZ000261b-ZOLU) issued by AstraZeneca UK Limited, which had appeared in The Pharmaceutical Journal, 17 January 2009 and included the following:

> 'The Medicines and Healthcare products Regulatory Agency (MHRA) recently reviewed the licence for goserelin 3.6 mg and 10.8 mg and updated the Summary of Product Characteristics (SmPC) to reflect these survival benefits. As such Section 5.1 of the goserelin SmPC details a wealth of survival data relating specifically to randomised controlled trials with goserelin.'

Zoladex was a leuteinising hormone releasing hormone analogue (LHRHa) indicated for certain types of cancer.

COMPLAINT

The MHRA alleged that reference in the advertisement to the MHRA was in breach of Clause 9.5 of the Code.

The MHRA referred to a previous case, Case AUTH/1794/2/06, involving Ipsen's product Decapeptyl (triptorelin) which had prompted AstraZeneca to contact the MHRA. The Therapeutic Review Group reviewed all LHRHas and amended the indications to ensure they were in accordance with current clinical guidelines and terminology.

The advertisement at issue gave AstraZeneca's perspective on the therapeutic review.

RESPONSE

AstraZeneca accepted that this genuine error was in breach of Clause 9.5 and unreservedly apologised to the MHRA. Measures had been taken to stop, where possible, any further publication of the advertisement at issue. The text would be amended. In addition, this case would be addressed at AstraZeneca's internal quarterly Code awareness training days.

AstraZeneca did not intend to suggest endorsement of Zoladex by the MHRA. The reference to the MHRA was intended to be a factual account of events and that this was a breach of Clause 9.5 was a genuine oversight.

AstraZeneca accepted that the therapeutic review was initially conducted to ensure that licences for the LHRHa class were in accordance with current clinical guidelines and terminology and that this followed a historical case. However, the additional changes to the Zoladex summary of product characteristics (SPC) to reflect survival benefits was agreed following further discussion with the MHRA after the initial class review. The advertisement referred to this most recent update of the SPC in July 2008.

AstraZeneca proposed to amend to, *inter alia*, remove all direct reference to the MHRA. The company would write directly to the MHRA to ensure that it agreed with the proposed amendments.

PANEL RULING

The Panel noted that Clause 9.5 prohibited reference in promotional material to, *inter alia*, the MHRA. The only exemption to this prohibition was if such reference was specifically required by the licensing authority. The MHRA had not specifically required AstraZeneca to include such a reference in its promotional material. The Panel therefore ruled a breach of Clause 9.5 as acknowledged by AstraZeneca.

Complaint received **27 January 2009**

Case completed **24 February 2009**

CASE AUTH/2206/2/09

VOLUNTARY ADMISSION BY ASTRAZENECA

Crestor email

AstraZeneca voluntarily admitted that, in response to a request for clarification about discounts, one of its dispensing account managers had sent an unapproved promotional email for Crestor (rosuvastatin) to a dispensing practice. The email contained promotional claims that were inaccurate, unbalanced and misleading.

AstraZeneca noted that the email was promotional but was not approved through review and certification by registered signatories and did not contain prescribing information.

The email contained the claim 'The start dose for ALL patients is 10mg …'. Although this was later qualified by the statement 'You can use 5mg in patients who can't tolerate a statin/the very elderly etc …', the claim was inaccurate, exaggerated and inconsistent with section 4.2 of the Crestor summary of product characteristics (SPC) which emphasised the recommendation of a 5mg start dose in certain patient groups. The email also contained the claims '85% to 90% of all patients should get to target on 10mg as it is so effective …' and 'Crestor is so well tolerated with so many fewer interactions than simva and atorva …' and 'is metabolised via the same pathway as prava making it much cleaner …' which were exaggerated and could not be substantiated. Two PowerPoint slides attached to the email showing Crestor data in the form of graphs although accurate, could be construed as promotion and had not been approved for such use and did not contain prescribing information.

The detailed response from AstraZeneca is given below.

The email from the dispensing account manager to the dispensary manager began by discussing potential discounts. The third paragraph read 'The start dose for ALL patients is 10mg as 10mg is equivalent to simva 80mg and atorva 40mg. 85% to 90% of all patients should get to target on 10mg as it is so effective. You can use 5mg in patients who can't tolerate a statin/the very elderly etc but it is the same price as 10mg and Crestor is so well tolerated with so many fewer interactions than simva and atorva (is metabolised via the same pathway as prava making it much cleaner) most use 10mg straight off'.

The Panel noted that the email discussed the efficacy and tolerability of Crestor. It did not contain prescribing information nor had it been certified. Breaches of the Code were ruled.

Section 4.2 of the Crestor SPC stated that the 'recommended start dose is 5mg or 10mg orally once daily in both statin naïve or patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions'. The 5mg dose was the recommended start dose in patients over 70 years, patients with moderate renal impairment and patients with predisposing factors to myopathy. The Panel considered that the claim 'The start dose for ALL patients is 10mg…' was misleading, incapable of substantiation, exaggerated and inconsistent with the SPC. Breaches of the Code were ruled.

The Panel considered that the claim '85% to 90% of all patients get to target on 10mg as it is so effective' was incapable of substantiation and exaggerated as acknowledged by AstraZeneca. Breaches of the Code were ruled.

The email featured a claim which compared the tolerability of Crestor with that of simvastatin and atorvastatin: 'Crestor is so well tolerated with so many fewer interactions than simva and atorva (is metabolised via the same pathway as prava making it much cleaner) …'. The Panel considered that this claim was exaggerated and could not be substantiated as acknowledged by AstraZeneca. Breaches of the Code were ruled.

The Panel considered that the two PowerPoint slides attached to the email were promotional; they each contained graphs which favourably compared Crestor with other statins and one featured the product logo. The Panel noted AstraZeneca's acknowledgement that they had not been approved for promotional use and did not contain prescribing information. Breaches of the Code were ruled.

The Panel considered that overall high standards had not been maintained. A breach of the Code was ruled. The Panel did not consider that the circumstances warranted a breach of Clause 2 which indicated particular censure and was reserved for such use.

AstraZeneca voluntarily admitted that one of its dispensing account managers had sent an unapproved promotional email for Crestor (rosuvastatin) to a health professional. The email contained promotional claims that were inaccurate, unbalanced and misleading.

COMPLAINT

AstraZeneca explained that the email was sent in

response to an enquiry from a dispensary manager of a dispensing practice on 13 November. The dispensary manager wanted clarification on discounts offered on 10mg and 20mg rosuvastatin and also asked, 'Do you swap simvastatin 40mg to rosuvastatin 20mg?'

Whilst there had been no external complaints in relation to this email, fortunately another employee in the same team brought this matter to the attention of their line manager who referred the correspondence to the compliance department.

Following this notification, corrective correspondence was sent to the practice dispensary manager to clarify all issues with an offer for a face-to-face follow up to address any potential misunderstandings. AstraZeneca submitted that, following a full internal investigation, a comprehensive range of proactive activities had been completed with the individual concerned. The company considered that this was an isolated incident, but nevertheless had taken the opportunity to schedule other activities as part of ongoing compliance training.

AstraZeneca outlined the corrective measures taken.

Internal measures:

- The individual concerned had undergone one-to-one retraining on the Code and company policies with specific focus on the requirements around email communication. Appropriate action in accordance with company policy was taken against the individual to reflect this serious mistake. Although this was an isolated incident, all dispensing account managers, sales management and representatives had been reminded about the Code requirements for emails. By the end of February 2009 they would also receive an update to their Field Guide which was a hard copy folder that all representatives carried containing company policies and guidance on compliant conduct. Face-to-face Code and role specific retraining would take place for all dispensing account managers in February 2009.

External Measures:

- AstraZeneca wrote to the practice concerned noting the errors and providing corrected information. A follow-up meeting and/or further information was offered if required. To date no request had been received from the practice. In addition AstraZeneca self reported to the PMCPA.

The email in question:

- Was promotional in nature but was not approved through review and certification by registered signatories.
- Contained the claim 'The start dose for ALL patients is 10mg …'. Although this was later qualified by the statement 'You can use 5mg in patients who can't tolerate a statin/the very elderly etc …', the claim was inaccurate, exaggerated and inconsistent with section 4.2 of the Crestor summary of product characteristics (SPC) which emphasised the recommendation of a 5mg start dose in certain patient groups.
- Contained the claim '85% to 90% of all patients should get to target on 10mg as it is so effective …'. The claim was not capable of substantiation and was exaggerated.
- Contained the claim 'Crestor is so well tolerated with so many fewer interactions than simva and atorva …' and 'is metabolised via the same pathway as prava making it much cleaner …'. These were exaggerated safety claims that could not be substantiated.
- Did not contain prescribing information.
- Contained a PowerPoint attachment consisting of 2 slides showing Crestor data in the form of graphs. Although there were no promotional claims and the data was accurate, the slides could be construed as promotion and had not been approved for such use and they did not contain prescribing information.

AstraZeneca submitted that the following points should be taken into account.

- The dispensing account manager had confirmed that this was an isolated incident and recognised that in her desire to reply quickly (within an hour of the request) and helpfully, she had exceeded her authority. The lapse of judgement was probably compounded by the fact that the dispensary manager and the dispensing account manager had a very close family connection. However, the email was sent in a business context and so the Code applied.
- In April 2008 the dispensing account manager passed an annual test on the updated company policy relating to sales and marketing practices which included the requirements of the Code. The dispensing account manager also passed a test on the AstraZeneca global code of conduct which required all employees to adhere to all relevant company and external codes.
- There had been no external complaint in relation to the email and any possibility for external misunderstanding had been minimised by the appropriate action taken.

This investigation and outcome was tabled at AstraZeneca's internal governance meeting on 27 January 2009. A range of additional actions were discussed and it was agreed that a further meeting should be convened as a matter of urgency to agree a clear corrective action plan. As a result, further additional requirements stipulated that reassurance must be provided that the whole dispensing account manager team, as well as the wider field force, continued to comply with the Code to ensure that similar incidents should not occur again. AstraZeneca undertook every measure to comply with the Code in both letter and spirit and considered that any breach was an

extremely serious matter. The governance committee would retain direct oversight of the actions to ensure they were implemented effectively and diligently.

AstraZeneca submitted that this incident was more than regrettable and all actions were being undertaken to ensure it did not happen again.

* * * * *

Paragraph 5.4 of the 2008 Constitution and Procedure provided that the Director should treat a voluntary admission as a complaint if it related to a potentially serious breach of the Code or if the company failed to take appropriate action to address the matter. Issuing uncertified material and promoting medicines by email were serious matters and the admission was accordingly treated as a complaint.

When writing to AstraZeneca the Authority asked it to respond in relation to the requirements of Clauses 2, 3.2, 4.1, 7.2, 7.4, 7.9, 7.10, 9.1 and 14.1 of the Code.

RESPONSE

In addition to its comments above AstraZeneca submitted that it took the Code extremely seriously and undertook every effort to comply with it in both letter and spirit. To this end, the company had robust and wide-ranging measures to ensure compliance with the Code through training, monitoring, approval and auditing processes. In addition, AstraZeneca strongly encouraged all employees to report any potential breaches of the Code to their manager or to the compliance functions. The company had dedicated independent telephone lines and a website to further facilitate such reporting.

It was this culture of openness and express commitment to the Code which gave an AstraZeneca employee the confidence to raise this matter internally and which the company had duly referred to the PMCPA. As part of this process, AstraZeneca accepted that the email in question was in breach of Clauses 3.2, 4.1, 7.2, 7.4, 7.9, 7.10 and 14.1.

As part of this process of self-reporting, a thorough review of the training processes in place for the individual who sent the email showed that they:

- passed the ABPI examination for representatives in July 1998
- underwent an AstraZeneca 'Initial Training Course' and validation (which included training on the Code) in January 2000
- passed an annual test on the company's updated policy relating to sales and marketing practices which included the Code, in April 2008
- passed a test on the AstraZeneca global code of conduct in August 2008

Despite the training provided by AstraZeneca, the dispensing account manager concerned sent an email that was in breach of the clauses referred to above. This was due to a genuine, though isolated, lapse of judgement probably compounded by the fact that the dispensary manager (to whom the email was sent) and the dispensing account manager had a very close family connection.

AstraZeneca did not believe that this matter warranted a ruling of breach of either Clause 9.1 or Clause 2. In relation to Clause 9.1, the individual concerned had received prior training from AstraZeneca and robust and rapid internal and external corrective actions were taken by AstraZeneca when it knew of the email. In addition, the email was not an unsolicited approach but was sent in response to a request by the dispensing practice manager, nor had the email caused any offence and the type, style and method of the communication was not such as to be considered unsuitable or distasteful.

In relation to a breach of Clause 2, it was important to note that this isolated email was only sent to a single recipient and that there had been no external complaint about it. These facts, together with the external corrective action taken meant that there was no question that the reputation of the industry had been damaged nor that confidence in the industry been reduced.

AstraZeneca provided an anonymised version of the original email request from the dispensary manager.

AstraZeneca stated that it took the Code extremely seriously and the governance committee (composed principally of the directors) would retain direct oversight of the corrective actions to ensure there was no recurrence.

PANEL RULING

The email from the dispensing account manager to the dispensary manager began by discussing potential discounts. The third paragraph read 'The start dose for ALL patients is 10mg as 10mg is equivalent to simva 80mg and atorva 40mg. 85% to 90% of all patients should get to target on 10mg as it is so effective. You can use 5mg in patients who can't tolerate a statin/the very elderly etc but it is the same price as 10mg and Crestor is so well tolerated with so many fewer interactions than simva and atorva (is metabolised via the same pathway as prava making it much cleaner) most use 10mg straight off'.

The Panel noted that the email was sent in response to an enquiry about discounts for Crestor. It was not clear whether the enquiry was solicited or not. The Panel considered that in any case the email in question could not take the benefit of the exemption in Clause 1.2 to the definition of promotion whereby replies to unsolicited enquiries

were exempt from the definition of promotion if, *inter alia*, they related solely to the subject matter of the enquiry and were not promotional in nature. The Panel noted that the email discussed the efficacy and tolerability of Crestor. It did not contain prescribing information nor had it been certified as required by Clause 14.1. Breaches of Clauses 4.1 and 14.1 were ruled.

Section 4.2 of the Crestor SPC stated that the 'recommended start dose is 5mg or 10mg orally once daily in both statin naïve or patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions'. The 5mg dose was the recommended start dose in patients over 70 years, patients with moderate renal impairment and patients with predisposing factors to myopathy. The Panel considered that the claim 'The start dose for ALL patients is 10mg…' was misleading, incapable of substantiation, exaggerated and inconsistent with the SPC. Breaches of Clauses 3.2, 7.2, 7.4 and 7.10 were ruled.

The Panel considered that the claim '85% to 90% of all patients get to target on 10mg as it is so effective' was incapable of substantiation and exaggerated as acknowledged by AstraZeneca. Breaches of Clauses 7.4 and 7.10 were ruled.

The email featured a claim which compared the tolerability of Crestor with that of simvastatin and atorvastatin: 'Crestor is so well tolerated with so many fewer interactions than simva and atorva (is metabolised via the same pathway as prava making it much cleaner) …'. The Panel considered that this claim was exaggerated and could not be substantiated as acknowledged by AstraZeneca. Breaches of Clauses 7.4, 7.9 and 7.10 were ruled.

The Panel noted the email attachment comprised two PowerPoint slides for Crestor. The Panel did not accept that the slides did not contain promotional claims as submitted by AstraZeneca; they each contained graphs which favourably compared Crestor with other statins. One of the slides featured the product logo. The Panel noted AstraZeneca's acknowledgement that they had not been approved for promotional use and did not contain prescribing information. Breaches of Clauses 14.1 and 4.1 were ruled.

The Panel considered that overall high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a breach of Clause 2 which indicated particular censure and was reserved for such use. No breach of Clause 2 was ruled.

Complaint received **11 February 2009**

Case completed **17 March 2009**

CASE AUTH/2207/2/09

CEPHALON v PROSTRAKAN

Promotion of Abstral

Cephalon alleged that the claim 'Rapid relief of breakthrough cancer pain from 10 minutes', used by ProStrakan to promote Abstral (sublingual fentanyl citrate tablet), was inconsistent with the particulars listed in the summary of product characteristics (SPC) in breach of the Code.

The detailed response from ProStrakan is given below.

The Panel noted that Section 5.1 of the Abstral SPC (Pharmacodynamics properties) stated that '…Abstral has been shown to induce significantly superior relief of breakthrough pain compared with placebo from 15 minutes after administration onwards…'. Section 4.2 of the SPC (Posology and method of administration) stated that 'if adequate analgesia is not obtained within 15-30 minutes of administration of a simple sublingual tablet, a second 100 microgram sublingual tablet may be administered'.

The Panel noted that the claim for 'Rapid relief of breakthrough cancer pain from 10 minutes' was based upon efficacy data from a study. Nonetheless the ten minute claim was inconsistent with the Abstral SPC and the Panel thus ruled a breach of the Code.

Cephalon (UK) Limited complained about the promotion of Abstral (sublingual fentanyl citrate tablet) by ProStrakan Ltd. The materials at issue were two leavepieces (refs MO17/0070 and MO17/0101). Inter-company dialogue had failed to resolve the issues.

Claim 'Rapid relief of breakthrough cancer pain from 10 minutes'

This claim was referenced to data on file – Study EN3267-005 in both leavepieces.

COMPLAINT

Cephalon alleged that the claim was inconsistent with the marketing authorization. Section 5.1 of the Abstral summary of product characteristics (SPC) stated:

> 'In patients with chronic pain on stable maintenance doses of opioids, Abstral has been shown to induce significantly superior relief of breakthrough pain compared to placebo from 15 minutes after administration onwards, …'.

Thus the claim for relief from 10 minutes implied statistical significance which was inconsistent with the particulars listed in the SPC in breach of Clause 3.2 of the Code.

RESPONSE

ProStrakan stated that the licensed indication for Abstral was 'Management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain'. ProStrakan also stated that breakthrough cancer pain, a transitory exacerbation of pain that occurred on a background of otherwise stable pain (Portenoy and Hagen 1990) was a common condition in cancer patients (Patt 1998). Breakthrough cancer pain was characterised by a rapid onset and short duration, often reaching peak intensity in as little as 3 minutes and lasting, on average, 30 minutes (Bennett *et al* 2005, Simmonds 1999). The maximum intensity of breakthrough cancer pain was often moderate to severe (Skinner *et al* 2006). It had a significant impact on patients' quality of life, including effects on patient activity, relationships and mood (Caraceni *et al* 2004, Portenoy and Hagen) and caused increased treatment costs (Fortner *et al* 2002).

Conventional treatment strategies for cancer pain comprised 24 hour analgesia to control background pain, with additional analgesics, such as immediate-release morphine, provided as needed to control episodes of breakthrough cancer pain (Bennett *et al*). However, many commonly used analgesics did not display a time-action profile suitable to match the rapid-onset, short-lived nature of breakthrough cancer pain (Bennett *et al*). The successful treatment of breakthrough cancer pain required fast-acting, potent analgesics; time to onset of analgesia was of key importance. ProStrakan was therefore committed to providing health professionals with the most recent and appropriate information about the efficacy of Abstral, and in particular onset of effect.

The potency and rapid absorption of oral transmucosal fentanyl products made them ideal for the treatment of breakthrough cancer pain but also conferred considerable clinical risk when used inappropriately. A recent US safety alert for Fentora (fentanyl buccal tablets) highlighted the serious and sometimes fatal consequences of inappropriate or inaccurate prescribing and use of these products. ProStrakan considered that the safety of patients using transmucosal fentanyl products such as Abstral was best served by providing prescribers with the most up-to-date information.

ProStrakan stated the information in Section 5.1 of the current Abstral SPC was derived from a Phase II

study, SuF 002; this was a Swedish-based, randomised, multicentre, double-blind, four-period crossover study conducted in opioid-tolerant male and female Caucasian patients with locally advanced or generalised cancer and breakthrough cancer pain (Lennernäs *et al* 2008). Patients took single doses of 100, 200 and 400mcg Abstral and placebo in a random order and without any dose titration. Twenty-three patients completed all four treatment periods; 15 did not complete the study according to protocol. The intent-to-treat (ITT) population comprised 27 patients, while 23 patients formed the per-protocol set (PPS). In the PPS, the shape of the time curve for mean pain intensity difference showed a significant overall improvement in pain intensity over the whole treatment period with Abstral 400mcg compared with placebo (8.57mm, p<0.001), with visual separation of the curves being seen as early as 5 minutes post-dose. These findings were replicated in the ITT population.

ProStrakan stated that improvement in pain intensity was greater with Abstral 400mcg compared with placebo, with this effect being evident at all time points assessed and becoming statistically significant from 15 minutes onwards post-dose (p=0.005).

ProStrakan stated that study EN3267-005 was a double-blind, randomised, placebo-controlled, multicentre study to evaluate the efficacy and safety of Abstral for the treatment of breakthrough pain in opioid-tolerant cancer patients followed by an up to 12-month non-randomised, open-label extension to assess long-term safety. In this study patients started the titration phase with 100mcg Abstral. If this dose was inadequate they moved to the next highest dose strength for the subsequent episode of breakthrough pain. This process continued through the available dose strengths of 100, 200, 300, 400, 600 and 800mcg until a patient identified a single effective Abstral dose that treated all episodes of breakthrough pain on 2 consecutive days. Following successful titration the patients were randomised to the double-blind phase where 10 doses of study medication were provided comprising 7 doses of Abstral (at the stable dose determined in the titration phase for that patient) and 3 matching placebo doses. Ninety-seven percent of the patients that completed the titration phase and entered the randomisation phase then elected to continue into the open label phase of the study where they continued to receive Abstral to treat breakthrough cancer pain for up to 12 months and safety data only was collected. The primary objective of the study was to compare the efficacy of Abstral with that of placebo as measured by the sum of pain intensity difference from baseline to 30 minutes after dosing. Secondary objectives included assessment of pain intensity difference, pain relief and rescue medication use.

ProStrakan stated that the efficacy phase data was analysed in December 2007 (study EN3267-005 data on file). The analysis of data from the ITT population (n=61) and the PP set (n=45) demonstrated that Abstral was superior to placebo in treating cancer breakthrough pain as measured by sum of pain intensity difference during a breakthrough episode.

ProStrakan stated that Abstral was shown to provide improved reduction in pain intensity from the first measured time point (10 minutes) that was significantly different to placebo (1.16 vs 0.88 respectively; p=0.0055). This statistically significant difference was also present at 15 minutes and was maintained to 60 minutes.

Following a comprehensive review of the EN3267-005 efficacy data, ProStrakan was confident in its robustness and validity and had made them available to UK health professionals caring for patients with breakthrough cancer pain. In December 2008 an abstract of the data was accepted for presentation at the World Institute of Pain meeting in March 2009 in New York (Rauck *et al* 2009). ProStrakan noted that this abstract referred to 'interim' results for this study. The efficacy data presented above and in the abstract were not interim. It was the safety data that was interim as the final safety dataset had not been fully analysed when the abstract was submitted.

Comparison of Phase II and Phase III studies and Abstral SPC

ProStrakan highlighted the key differences between the Phase II and Phase III studies and compared these with the current SPC for Abstral (table below). As this table showed, the Phase III study used the same starting dose, dose titration scheme and dose range as the current UK SPC for Abstral, in contrast to the Phase II study. Additionally, the Phase III study used a larger sample size and measured pain intensity in more than 5 times as many pain episodes than the Phase II study

	Phase II study	**Phase III study**	**Abstral SPC**
Sample size	27 patients	61 patients	
Number of pain episodes assessed per patient	1 per dose (4 total)	10	
Total pain episodes assessed	108	561	
Starting dose	100-400mcg	100mcg	100mcg
Dose range	100-400mcg	100-800mcg	100-800mcg
Ascending titration through available dose strengths (100, 200, 300, 400, 600 and 800mcg)	No	Yes	Yes

ProStrakan stated that the following data was derived from the EN3267-005 Phase III study and a further Phase III long-term safety study (EN3267-007) that used the same titration method as study 005 (study EN3267-005 and study EN3267-007 data on file). The Abstract Phase III dose data demonstrated that the full range of Abstral doses

was required to successfully treat breakthrough cancer pain. Of particular significance was that 48% of patients required final Abstral doses of either 600 or 800mcg (doses that were not used in the Phase II study). These results further indicated the importance of the Phase III data where all doses were assessed.

ProStrakan noted that the current SPC stated 'Abstral has been shown to induce significantly superior relief of breakthrough pain compared to placebo from 15 minutes after administration onwards' was based on data from the Phase II study. The EN3267-005 Phase III study also demonstrated pain relief at 15 minutes, therefore it did not contradict what was shown in the Phase II study, nor the current SPC. Additionally, the Phase III study showed that Abstral, when used correctly under the conditions specified in the current SPC (particularly starting at 100mcg, dose titrating and utilising the entire dose range of 100-800mcg where necessary), could result in significant pain relief from as early as 10 minutes. ProStrakan therefore considered it appropriate to make this information available to health professionals who were using Abstral as directed by the SPC.

ProStrakan stated that the Phase III data and the 10 minute claim were also plainly referenced in all materials as coming from the EN3267-005 study and were therefore clearly distinct from the data contained in the SPC.

ProStrakan noted that Clause 7.2 of the Code required all claims to be based on 'an up-to-date evaluation of all the evidence and reflect that evidence clearly'. By considering the Phase III data when formulating claims, ProStrakan believed it had acted in line with this requirement. Furthermore, the European Medicines Evaluation Agency's guideline on SPCs stated that in Section 5.1 'It may be appropriate to provide limited information, relevant to the prescriber…regarding pre-specified end points or clinical outcomes'. This section of the SPC was therefore not intended to be a definitive summary of all the efficacy data pertaining to a particular medicine.

In conclusion, ProStrakan denied a breach of Clause 3.2. As detailed above, the Phase III data was collected under conditions that were much more consistent with the dosage and administration stated in the current SPC than the Phase II study. The Phase III data also demonstrated efficacy at 15 minutes and was consequently not inconsistent with the current SPC. The Phase III data was therefore up-to-date, relevant and robust. As such, it was of central importance for health professionals treating breakthrough cancer pain. ProStrakan had therefore published this data and included it in its promotional materials in order to enhance the care of patients with this debilitating condition. ProStrakan firmly believed that, for the reasons outlined above, such behaviour did not contravene either the letter or the spirit of the Code.

PANEL RULING

The Panel noted that Section 5.1 of the Abstral SPC (Pharmacodynamic properties) stated that '… Abstral has been shown to induce significantly superior relief of breakthrough pain compared with placebo from 15 minutes after administration onwards …'. Section 4.2 of the SPC (Posology and method of administration) stated that 'if adequate analgesia is not obtained within 15-30 minutes of administration of a simple sublingual tablet, a second 100 microgram sublingual tablet may be administered'.

The Panel noted that the claim at issue 'Rapid relief of breakthrough cancer pain from 10 minutes' was based upon the efficacy data from study EN3267-005. Nonetheless the ten minute claim was inconsistent with the particulars listed in the Abstral SPC and the Panel thus ruled a breach of Clause 3.2 of the Code.

Complaint received **11 February 2009**

Case completed **16 March 2009**

HEALTH PROFESSIONAL v GILEAD SCIENCES

Unsolicited email

A health professional complained that he had received an unsolicited email from Gilead Sciences; he had not provided his email address to Gilead. The complainant had asked Gilead how it had obtained his personal email address and to seek confirmation that it would be removed from its mailing list. The complainant had had no reply.

The complainant noted that whilst the email did not relate to a particular product, it advertised a Gilead sponsored fellowship programme. The complainant alleged that use of his private email address for this purpose was in breach of the Code. More worrying, however, was the fact that the company had his email address.

The detailed response from Gilead is given below.

The Panel noted that the email in question informed recipients about the new Gilead UK and Ireland Fellowship Programme which was to largely replace an existing grants process. The aims of the programme were outlined and the reader was referred to an attached letter for more details. Neither the email nor the attached letter referred to any specific products. Reference was made to HIV, invasive fungal disease and chronic hepatitis B.

The Panel noted that the Code prohibited the use of email for promotional purposes without the prior permission of the recipient. The Panel considered that the email in question was non-promotional and in that regard it ruled no breach of the Code.

The Panel noted, from copies of emails provided by Gilead, that the complainant had contacted the company on 29 January requesting, *inter alia*, that his name be removed from the mailing list. Gilead replied the next day stating that the complainant's details would be removed from the medical director's business contacts list. The Panel ruled no breach of the Code.

COMPLAINT

A health professional complained that he had received an unsolicited email from Gilead Sciences Ltd; he had not provided his email address to Gilead. The complainant had written to Gilead to ask how it had obtained his personal email address and to seek confirmation that the address would be removed from its mailing list. The complainant had had no reply.

The complainant noted that whilst the email did not relate to a particular product, it did advertise a fellowship programme sponsored by Gilead. The complainant alleged that use of his private email address for this purpose was in breach of Clause 9.9 of the Code. More worrying, however, was the fact that the company had his email address.
In addition to Clause 9.9 cited by the complainant the Authority also requested Gilead to consider the requirements of Clause 9.1.

RESPONSE

Gilead submitted that the non-promotional email in question was sent by the medical director to a broad group of health professionals whom he emailed regularly; a copy of the original email and attachment was provided.

The complainant's email address was inadvertently included in the distribution list of recipients. On receipt of a complaint from this recipient, 30 January 2009, an apology was sent immediately with confirmation that his name had been removed from the distribution list. Unfortunately, it appeared that this never reached the complainant and he subsequently raised the matter with the Authority.

The subject of the email sent on 28 of January was the launch of the 'Gilead UK and Ireland Fellowship'. This was a new initiative to largely replace the company's existing grants process. The programme aimed to support the development, exploration and dissemination of best practice which enhanced patient care in HIV, invasive fungal disease and chronic hepatitis B. Grants would be awarded to individual organisations or groups of healthcare providers within a locality.

Gilead provided a copy of its 'guidance to applicants' leaflet sent to all who expressed an interest in the fellowship programme.

Gilead submitted that complaint fell outside of the scope of the Code as set out in Clause 1, as the email was non-promotional.

Gilead accepted that the email was erroneously sent to the complainant. In this regard, the company had fallen below the usual high standards which set itself and unreservedly apologised. The complainant's name had been removed from Gilead's distribution list to ensure that this could not happen again.

PANEL RULING

The Panel noted that the email in question informed recipients about the new Gilead UK and Ireland

Fellowship Programme which was to largely replace the existing grants process. The aims of the programme were outlined; it appeared that it would support disease areas in which Gilead had a commercial interest. The reader was referred to an attached letter for more details. Neither the email nor the attached letter referred to any specific products. Reference was made to HIV, invasive fungal disease and chronic hepatitis B.

The Panel noted that Clause 9.9 prohibited the use of email for promotional purposes without the prior permission of the recipient. The Panel considered that the email in question was non-promotional and in that regard it ruled no breach of Clause 9.9.

The Panel noted, from copies of emails provided by Gilead, that the complainant had contacted the company on 29 January requesting, *inter alia*, that his name be removed from the mailing list. Gilead replied the next day stating that his details would be removed from the medical director's business contacts list. The Panel considered that in this regard high standards had been maintained. No breach of Clause 9.1 was ruled.

Complaint received **16 February 2009**

Case completed **23 March 2009**

ANONYMOUS v ASTRAZENECA

Conduct of representative

An anonymous and uncontactable general practitioner complained about the conduct of one of AstraZeneca's representatives and stated that he was shocked at what the company allowed its representatives to get away with.

The complainant stated that many of his colleagues were heavily influenced by the representative and AstraZeneca. The representative had owned and run a very popular local bar restaurant for several years which was frequented by many medical professionals, especially on certain days when it was open house for all. Free drinks were given to many of the complainant's colleagues and the representative sponsored a local health professional's sports team. The complainant felt very uncomfortable with this, especially as all of AstraZeneca's competitors had such strict rules to adhere to. Did these not apply to AstraZeneca?

The representative had also recently set up a consumables company supplying many local GP practices. Was this not a conflict of interest?

It was rumoured that the representative funded his entertainment activities from running medical meetings at the two venues he owned. Was this not corrupt?

A copy of an article discussing the representative and his business interests, which did not mention AstraZeneca was provided.

The detailed response from AstraZeneca is given below.

The Panel considered that the fact that the representative was a part owner of venues where meetings with health professionals took place was not a breach of the Code per se. The arrangements would have to comply with the Code. No allegations had been made about specific meetings. With regard to sponsorship of the local health professionals' sports team, the Panel noted that the representative had done this in his capacity as a local business man, not as a local medical representative. Nonetheless, the Panel was concerned about the impression created by the arrangements; the representative would be seen as inevitably benefiting from interactions with health professionals which if funded by a pharmaceutical company were very likely to be in breach of the Code.

In the Panel's view it was difficult for medical representatives to have two different types of professional relationships with health professionals without there being the perception of a conflict of interest.

The Panel considered that the activities at issue were potentially subject to the Code. It was a question of whether or not they were in breach of the Code.

The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. The Panel had some concerns about the arrangements particularly the alleged lack of distinction between the role of a representative and the other business activities of the representative as there was a possible conflict of interest. The Panel considered that the allegation was a serious one but it did not consider that evidence had been provided by the complainant to show that on the balance of probabilities the representative in question had conducted inappropriate meetings as alleged or that the other activities listed were unacceptable in relation to the Code and thus no breach of the Code was ruled.

An anonymous and uncontactable general practitioner wrote to AstraZeneca UK Limited to complain about the conduct of one of its named representatives. The complainant sent the ABPI a copy of his letter to AstraZeneca and that letter was passed to the PMCPA and dealt with as a complaint under the Code. Attached to the letter was a transcript of an article which had appeared in a local newspaper, together with what appeared to be a printed webpage giving brief details of a company which could supply, *inter alia*, washroom supplies and medical products.

COMPLAINT

The general practitioner was somewhat shocked at the behaviour AstraZeneca allowed its representatives to get away with. The complainant had known the representative for many years and had always found him pleasant. He seemed to have a good relationship with the complainant's colleagues.

The complainant stated that many of his colleagues were heavily influenced by the representative and AstraZeneca. The representative had owned and run a very popular local bar restaurant for several years. This was frequented by many medical professionals, especially on certain days when it was open house for all. Free drinks were given to many of the complainant's colleagues and the representative sponsored a local health professionals' sports team. The complainant felt very uncomfortable with this, especially as all of AstraZeneca's competitors had such strict rules to adhere to. Did these not apply to AstraZeneca?

The representative had also recently set up a consumables company supplying many of the local GP practices with items. Was this not a conflict of interest?

It was rumoured that the representative funded his various entertainment activities from running various medical meetings at either his bar restaurant, or another venue he owned. Was this not corrupt?

The complainant thought in the current climate where the vast majority of pharmaceutical companies were struggling to give pens away, AstraZeneca's behaviour in employing and turning a blind eye to the representative was a disgrace.

A copy of an article discussing the representative and his business interests, which did not mention AstraZeneca was provided.

AstraZeneca was asked to respond in relation to Clauses 2, 9.1, 15.2 and 19.1 of the Code.

RESPONSE

AstraZeneca noted that the complainant raised several general concerns without always providing details of specific activities or dates. However, as far as was possible, the company had addressed each of the points raised.

AstraZeneca confirmed that the sales representative in question had been employed by the company for many years.

In the course of its investigation AstraZeneca had interviewed the representative as well as his first line, second line, third line and previous first line managers to establish the nature, scale and activities of the various businesses referred to by the complainant. In addition, AstraZeneca established the nature of the relationship between AstraZeneca and these businesses.

The company's meetings database (records were available from September 2004 onwards) was searched to identify all AstraZeneca meetings held in the named venues and all meetings organised by the representative at any other venues, for all time periods available. These records were scrutinised for compliance with the Code as were expense records for the representative, and any other representative who used those venues.

Finance databases were searched to establish any other payments made to these businesses by AstraZeneca.

AstraZeneca's investigation had established that the two establishments operated under the ownership of a company which had been part owned by the representative for almost 10 years. One establishment was a private members (1200 members) bar and restaurant with meetings facilities that were used by the pharmaceutical industry amongst others. The other establishment was a bar and restaurant, with facilities for private functions and business meetings. The consumables company was also part owned by the representative and provided a range of supplies for the catering and licensing trades including washroom supplies.

AstraZeneca noted that the greater part of the complaint appeared to be concerned with the possible commercial conflict of interest between the various businesses owned by the representative and AstraZeneca. Furthermore, that this was 'corrupt' and that, by implication, the representative had accrued inappropriate personal benefit. However, the representative had previously declared his commercial interest to AstraZeneca in line with the company's internal processes for declaring conflicts of interest. AstraZeneca did not believe this aspect of the complaint was in the scope of the Code.

Regardless of scope, AstraZeneca addressed what appeared to be the specific allegations as follows:

1 '… shocked at the behaviour AstraZeneca allowed its representatives to get away with'.

AstraZeneca noted the plural in 'representatives' even though only one representative was referred to. No specific detail was given in the complainant's letter but AstraZeneca assumed the 'behaviour' complained about were the activities related to the representative and addressed below.

2 '…many of his colleagues were heavily influenced by the representative and AstraZeneca. The representative had owned and run a very popular local bar restaurant for several years. This was frequented by many medical professionals, especially on certain days when it was open house for all. The representative gave free drinks to many of the complainant's colleagues …'.

AstraZeneca believed that the allegation here was that, in effect, AstraZeneca had provided inappropriate hospitality to health professionals at establishments part owned by the representative and that this had influenced their prescribing behaviour such as to constitute an inducement to prescribe.

The complainant did not provide specific dates of activities or name venues for these activities. However, AstraZeneca established that between September 2004 to March 2009, it had funded 129 meetings that involved health professionals at the private members club and 3 meetings at bar/restaurant. Of these, 37 were held in the last 18 months at the private members club and 3 at the bar/restaurant. All relevant company records for each of these meetings were scrutinised to judge their adherence with AstraZeneca External Meetings Policy. Both were modest establishments with suitable private meetings facilities for medical

educational meetings. They were not extravagant, deluxe or luxurious. They did not contain any sporting or entertainment facilities. (The club hosted a live band once or twice a year, but this had never been during an AstraZeneca meeting and nor was the club renowned for entertainment). AstraZeneca did not believe that the venues in themselves would have been a greater attraction for delegates to AstraZeneca meetings than the content of the meetings. Costs and arrangements for the 129 meetings at the private members club and the 3 meetings at the bar/restaurant were checked using the company meetings database and the expenses of the representative and all other company personnel who used these venues. The cost per head of the subsistence at all of these meetings did not exceed the AstraZeneca External Meetings Policy maximum allowable limits for lunch or dinner. Where health professionals were employed to speak at meetings the honoraria paid were in line with AstraZeneca policy guidance.

All 40 meetings held in the past 18 months at these venues either had a clear educational content, as evidenced by agendas retained in the meetings records, or they had a business purpose (of which there were 10) and were in line with the Business Meetings section of the AstraZeneca External Meetings Policy. An example of a 'business purpose' was a non-promotional discussion of future collaborative work with a health professional.

The costs for drinks for health professionals at these meetings were included in the per head subsistence costs and were in line with AstraZeneca policy. There was no evidence that further free drinks were offered or given to doctors at AstraZeneca educational meetings by the representative and this allegation was denied by all individuals interviewed. Where health professionals frequented either establishment on private occasions, they might have been offered free drinks on a discretionary basis by the staff. However, the representative was very clear that offering free drinks did not make commercial sense in relation to his restaurant business and certainly not by targeting specific customer groups. In addition it was unlikely that the staff would have known whether customers were health professionals or not.

There was no evidence that when health professionals received drinks on private occasions the drinks were perceived to be given on behalf of AstraZeneca or that the representative specifically targeted health professionals for such drinks in return for a spoken or unspoken influence on prescribing.

There was no evidence that spouses or family members of health professionals attended either AstraZeneca educational/business meetings at the private members club or the subsistence meals associated with them.

There was no evidence that the representative had ever discussed or offered health professionals free or discounted products from his companies during the course of AstraZeneca business with them (for example during one-to-one sales calls or AstraZeneca educational meetings). There was no evidence that the representative had exploited his access to health professionals during AstraZeneca sales calls to them, for the purpose of securing their attendance at his restaurants in a private capacity on a separate occasion. Conversely, there was no evidence that the representative had initiated discussion of AstraZeneca related matters with health professionals when they visited his restaurants in a private capacity.

AstraZeneca noted that it was only one of several pharmaceutical companies that used the private members club restaurant for educational meetings. There was no evidence that health professionals at AstraZeneca meetings were given preferential treatment compared with those attending other pharmaceutical companies' meetings.

For the purposes of attendance at any educational or business meetings, delegates from AstraZeneca and other pharmaceutical companies were not charged an entrance fee, nor were they given free membership of the club.

The complainant did not define the term '… open house for all …'. However, it might relate to the fact that the venue referred to was normally a members only club, but that on some occasions personal friends and some non-members were admitted. Players from the sports team were, on occasion, allowed admission for a day usually following a match. This was at the representative's discretion on occasions unrelated to AstraZeneca educational meetings or other company related business.

Since there was no evidence that inappropriate hospitality was given at any of the AstraZeneca meetings at these venues, the company did not believe that there could have been an inducement to prescribe. AstraZeneca therefore did not believe that there had been a breach of Clause 19.1.

3 Sponsorship of a sports team

AstraZeneca had never sponsored the sports team; company policy precluded this manner of support. AstraZeneca understood that the representative had coached this club for many years and more recently he had supported it with financial sponsorship of approximately £200 per year. However, he was approached for this support in his capacity as part owner of the members club and not in the course of his work for AstraZeneca. The funds were supplied by the private members club in return, on some occasions, for a club badge on the players' kit. There was no evidence to suggest that the team perceived support from the representative as being on behalf of AstraZeneca.

4 'The representative had also recently set up a consumables company supplying many of the local GP practices with items. Was this not a conflict of interest?'.

AstraZeneca confirmed that the representative part owned a supplies company.

AstraZeneca believed that part of the nature of the allegation was that the dual interests of the representative in this business, whilst also being an AstraZeneca employee, represented a potential financial risk to AstraZeneca with regard to the fair procurement of such businesses. As indicated above, it did not consider that this aspect of the complaint was in the scope of the Code.

It was also possible that the complainant was alleging that GP practices had received 'consumables' on favourable grounds for the purpose of influencing their prescribing in favour of AstraZeneca. However, only two practices had been supplied by the company and this was on terms comparable to other non-medical recipients who constituted the majority of the company's customers. There was no evidence that any GP practices or the health professionals or administrators at them perceived that they were receiving supplies from the supply company with any form of involvement or expectation from AstraZeneca.

5 'It was rumoured that the representative funded his various entertainment activities from running various medical meetings at either his bar restaurant, or another venue he owned. Was this not corrupt?'.

AstraZeneca believed that part of the allegation here was that the dual interests of the representative in this business, whilst also being an AstraZeneca employee, represented a potential financial risk to AstraZeneca with regard to the fair procurement of such businesses. The representative had submitted his interests in the members club restaurant to AstraZeneca and followed its process for considering conflicts of interest. As indicated above, AstraZeneca did not consider that this aspect of the complaint was in the scope of the Code.

6 A newspaper article discussing the representative and his business, which did not mention AstraZeneca.

The representative owned or part owned two establishments and a supply company. AstraZeneca had no financial ownership, oversight or involvement in the running of these companies. Apart from the medical educational meetings funded at the establishments by AstraZeneca, there was no relationship between AstraZeneca and these companies. That was why this article did not mention AstraZeneca and it would be alarming if it did. In addition, AstraZeneca did not have sight of or knowledge of this article before its release, nor any reason to have such sight or knowledge.

In the course of arranging AstraZeneca meetings, the representative had followed the AstraZeneca meetings policy and internal conflict of interest disclosure processes. The result was a series of meetings at the venues for which there was no evidence that hospitality was excessive or that it influenced health professionals. There was also no evidence that AstraZeneca related matters were discussed with health professionals when they visited these restaurants in a private capacity. Therefore, AstraZeneca did not believe that there had been a breach of Clauses 15.2 or 9.1.

Health professionals had frequented these restaurants for more than 10 years and educational meetings (by many companies) had been held there for a similar period without any evidence that pharmaceutical company business and restaurant related business had not been adequately separated.

Despite the long duration and scale of the representative's activities, the complainant's concerns were an isolated instance and were not backed up by information on specific dates or events. Therefore, AstraZeneca did not believe there had been a breach of Clause 2.

However, since there had been an external complaint, AstraZeneca would look again at this specific activity and the wider issue of conflict of interest. In addition, a reminder would be sent to the organisation, as a follow up to the business wide sign-off of the Global Code of Conduct (which contained the conflict of interest policy) that was conducted during the second half of 2008.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. When a general allegation had been made about a representative's conduct it was difficult to determine precisely what had occurred. In this instance there were no details about specific meetings and no way to ask the complainant for more information. AstraZeneca submitted that all the meetings in which the representative had a business interest in the venue, were in accordance with the Code.

Companies had to be vigilant when a representative's personal business interests involved dealing with health professionals. The contractual relationship between AstraZeneca and its employee was not a matter for the Code. The Panel noted that the representative had declared his interests to AstraZeneca in line with company policy. The Panel considered that whilst the company might be clear about the representative's distinct roles such a distinction might not be clear to third parties. The company should thus be mindful of the impression created by such activities and ensure that activities potentially within the scope of the Code stood up to scrutiny and complied with the Code.

The Panel considered that the fact that the representative was a part owner of venues where meetings with health professionals took place was

not a breach of the Code per se. The arrangements would have to comply with the Code. No allegations had been made about specific meetings. With regard to sponsorship of the local health professionals' sports team, the Panel noted that the representative had done this in his capacity as a local business man, not as a local medical representative. Nonetheless, the Panel was concerned about the impression created by the arrangements; the representative would be seen as inevitably benefiting from interactions with health professionals which if funded by a pharmaceutical company were very likely to be in breach of the Code.

In the Panel's view it was difficult for medical representatives to have two different types of professional relationships with health professionals without there being the perception of a conflict of interest.

The Panel considered that the activities at issue were potentially subject to the Code. It was a question of whether or not they were in breach of the Code.

The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. The Panel had some concerns about the arrangements particularly the alleged lack of distinction between the role of a representative and the other business activities of the representative as there was a possible conflict of interest. The Panel considered that the allegation was a serious one but it did not consider that evidence had been provided by the complainant to show that on the balance of probabilities the representative in question had conducted inappropriate meetings as alleged or that the other activities listed were unacceptable in relation to the Code and thus no breach of Clauses 9.1, 19.1 and 2 were ruled.

Complaint received **2 March 2009**

Case completed **27 March 2009**

CASE AUTH/2211/3/09

GENERAL PRACTITIONER v BOEHRINGER INGELHEIM

Micardis and Micardis Plus journal advertisement

A general practitioner complained about a journal advertisement for Micardis (telmisartan) and Micardis Plus (telmisartan and hydrochlorothiazide) issued by Boehringer Ingelheim which appeared in Prescriber. Telmisartan was an angiotensin II antagonist (AIIA) and hydrochlorothiazide was a diuretic. The advertisement featured a photograph of a man apparently rowing a canoe-like boat on a rough sea. The headline read 'You can't know what will happen tomorrow …'. Then, beneath the photograph the headline continued '… but with hypertension, you do have the POWER to be prepared for it …'. Beneath the claim were the product logos for Micardis and Micardis Plus.

The complainant alleged that the claim 'You can't know what will happen tomorrow … but with hypertension, you do have the POWER to be prepared for it … Micardis and Micardis Plus' was misleading, exaggerated and demonstrated an irresponsible approach to the promotion of prescription only medicines.

Micardis and Micardis Plus were solely indicated for the treatment of essential hypertension in adults. In contrast other medicines in the same class, such as candesartan, were additionally, indicated for the treatment of heart failure and left ventricular systolic dysfunction, a recognised potential future cardiovascular outcome associated with uncontrolled hypertension.

Readers, however, would reasonably assume from the reference in the claim to unspecified future events, that Micardis and Micardis Plus not only treated hypertension, but could also prevent/reduce the future occurrence of all potential events associated with essential hypertension.

This claim referred to an unqualified generalisation that could not be substantiated

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that both Micardis and Micardis Plus were indicated solely for the treatment of essential hypertension. The Panel noted Boehringer Ingelheim's submission that the goal of antihypertensive therapy was the eventual reduction in cardiovascular morbidity and mortality. The summary of product characteristics (SPC) for each product, however, stated that the effects of the medicine on mortality and cardiovascular morbidity were currently unknown.

The Panel considered that the claim 'You can't know what will happen tomorrow … but with hypertension, you do have the POWER to be prepared for it …' implied that Micardis and Micardis Plus had some beneficial effects on the long-term consequences of hypertension ie cardiovascular morbidity and mortality. 'You can't know what will happen tomorrow …' implied some event other than continuing hypertension and the second half of the claim implied efficacy in that regard. The Panel considered, however, that such an implication was misleading and inconsistent with the SPCs. The Panel considered that the claim was exaggerated and could not be substantiated. Breaches of the Code were ruled.

A general practitioner complained about a journal advertisement for Micardis (telmisartan) and Micardis Plus (telmisartan and hydrochlorothiazide) (ref MIC2508d) issued by Boehringer Ingelheim Limited which appeared in Prescriber, 19 February. Telmisartan was an angiotensin II antagonist and hydrochlorothiazide was a diuretic. The advertisement featured a photograph of a man apparently rowing a canoe-like boat on a rough sea. The headline read 'You can't know what will happen tomorrow…'. Then, beneath the photograph the headline continued '… but with hypertension, you do have the POWER to be prepared for it…'. Beneath the claim were the product logos for Micardis and Micardis Plus.

COMPLAINT

The complainant alleged that the claim 'You can't know what will happen tomorrow ….but with hypertension, you do have the POWER to be prepared for it…Micardis and Micardis Plus' was misleading and exaggerated; it demonstrated an irresponsible approach to the promotion of prescription only medicines.

Micardis and Micardis Plus were solely indicated for the treatment of essential hypertension in adults. In contrast other medicines in the same class, such as candesartan, were additionally, indicated for the treatment of heart failure and left ventricular systolic dysfunction, a recognised potential future cardiovascular outcome associated with uncontrolled hypertension.

The reference in the claim to unspecified future events, presumably those relating to cardiovascular morbidity and mortality or health-outcome events such as hospitalisation, in

relation to the power to be prepared for these events invited readers to reasonably surmise that Micardis and Micardis Plus were not only efficacious in treating hypertension, but by virtue of their effectiveness/potency, they could also prevent/reduce the future occurrence of all potential events associated with essential hypertension which included mortality, heart failure, stroke, acute coronary syndromes, health-outcome events amongst others.

When writing to Boehringer Ingelheim the Authority asked it to respond in relation to Clauses 3.2, 7.2, 7.4 and 7.10 of the Code.

RESPONSE

Boehringer Ingelheim considered that the claim 'You can't know what will happen tomorrow …but with hypertension, you do have the power to be prepared for it' promoted Micardis and Micardis Plus in a manner consistent with their marketing authorizations in line with Clause 3.2.

The context of the claim was entirely clear and was the condition for which Micardis and Micardis Plus were both licensed: '…but with **hypertension**, you do have the power…' (emphasis added) and Boehringer Ingelheim did not consider that the claim was misleading or in breach of Clauses 3.2 and 7.2. There was no mention of unspecified future events in the advertisement.

The claim referred to treating hypertension effectively now and in the future and, in the context of the current objectives of therapy, Boehringer Ingelheim considered that effective, 24 hour control of blood pressure in hypertension was entirely consistent with this. The advertisement made no claims with regard to the reduction, avoidance of, or any other effect on, future events.

Boehringer Ingelheim did not consider that the advertisement contained a claim that was 'an unqualified generalisation that could not be substantiated' as alleged. The claim was not exaggerated or generalised since it referred to 'hypertension' and in terms of substantiation, in line with Clauses 7.4 and 7.10, there was a large body of evidence demonstrating the efficacy ('power') of Micardis in the treatment of hypertension eg in comparison with other angiotensin II antagonists (Lacourière *et al* 2004, Smith *et al* 2003) or ACE inhibitors (Williams *et al* 2009), and MicardisPlus in comparison with valsartan/hydrochlorothiazide (White *et al* 2006).

It was widely accepted that the goal of hypertension treatment was not simply the reduction of hypertension in and of itself, but the eventual reduction of cardiovascular morbidity and mortality as indicated within various UK clinical guidelines:

- National Institute for Health and Clinical Excellence (NICE) guidelines for the 'Management of hypertension in adults in primary care'

  'Hypertension is a major but modifiable contributory factor in cardiovascular disease (CVD) such as stroke and coronary heart disease (CHD). The object of this guideline is to decrease cardiovascular morbidity and mortality resulting from these diseases.'

- Joint British Societies' Guidelines on 'Prevention of Cardiovascular disease in Clinical Practice'.

  '… total CVD risk management is emphasised in order to maximise CVD risk reduction, of which lowering blood pressure is one important component. Data from many randomised clinical trials provide compelling evidence of the effectiveness of antihypertensive therapy at reducing the risk of CVD. A reduction in blood pressure by an average of 12/6 mmHg can be expected to reduce stroke by 40% and CHD by 20%.'

In summary, Boehringer Ingelheim considered that the claim in question was clearly specific to hypertension, and that the claimed 'power' for Micardis and Micardis Plus in the treatment of hypertension could be substantiated. Boehringer Ingelheim, therefore, did not consider that the claim was misleading, or exaggerated or that it demonstrated an irresponsible approach to the promotion of prescription only medicines as alleged.

PANEL RULING

The Panel noted that both Micardis and Micardis Plus were indicated solely for the treatment of essential hypertension. The Panel noted Boehringer Ingelheim's submission that the goal of antihypertensive therapy was the eventual reduction in cardiovascular morbidity and mortality. Section 5.1, Pharmacodynamic properties, of the summary of product characteristics (SPC) for each product, however, stated that the effects of the medicine on mortality and cardiovascular morbidity were currently unknown.

The Panel considered that the claim 'You can't know what will happen tomorrow … but with hypertension, you do have the POWER to be prepared for it …' implied that Micardis and Micardis Plus had some beneficial effects on the long-term consequences of hypertension ie cardiovascular morbidity and mortality. 'You can't know what will happen tomorrow …' implied some event other than continuing hypertension and the second half of the claim implied efficacy in that regard. The Panel considered, however, that such an implication was misleading and

inconsistent with the particulars listed in the SPCs. Breaches of Clauses 3.2 and 7.2 were ruled. The data supplied by Boehringer Ingelheim in support of the claim demonstrated the hypertensive efficacy of Micardis and Micardis Plus; the studies did not set out to investigate any cardio-protective effect. The Panel considered that the claim was exaggerated and could not be substantiated. Breaches of Clauses 7.10 and 7.4 were ruled.

Complaint received **2 March 2009**

Case completed **30 March 2009**

ANONYMOUS DOCTOR v LILLY and BOEHRINGER INGELHEIM

Sponsored supplement

An anonymous doctor complained about a journal supplement distributed with an issue of Progress in Neurology and Psychiatry. The material in question was described as a report from the 2008 UK Psychiatry Forum and as 'A Progress supplement sponsored by Eli Lilly and Boehringer Ingelheim'. Prescribing information for Cymbalta (duloxetine) and Zyprexa (olanzapine) was included.

The complainant noted that the supplement had been produced to look exactly like the actual journal. There was only a small, easily missed statement at the bottom of the supplement indicating sponsorship by a pharmaceutical company.

From the supplement it appeared that the UK Psychiatry Forum was a body of some significant standing which was alleged to be misleading. The forum was an independent body but the complainant was not aware that it held any major impact in psychiatry academia or otherwise. It was not of any regulatory significance or responsible for any nationally implemented guidelines.

The complainant stated that the actual event that was reported was questionable. At a Lilly promotional meeting in Spain last year (s)he had heard all the authors speak in exactly the same order, giving exactly the same talks as in the report. The complainant alleged that the supplement thus misreported the actual event. The material was misleading and appeared to be disguised promotion.

The complainant noted that the supplement detailed a case of atypical depression. According to the Cymbalta summary of product characteristics (SPC), it was not licensed for atypical depression. This was off-licence promotion.

The complainant alleged that the supplement, in its entirety, was misleading and it was disappointing that the journal concerned had allowed it to be printed. Furthermore, such actions brought disrepute to an industry at a time when transparency in the NHS and industry was vital to ensure trusting mutual collaborative practice that benefitted the service provided to patients.

The detailed responses from Lilly and Boehringer Ingelheim are given below.

The Panel noted that the material in question provided the proceedings of a promotional symposium run by Lilly and Boehringer Ingelheim at the time of the European College of Neuropsychopharmacology (ECNP) congress, in the form of a journal supplement. The 90 delegates to the Lilly and Boehringer Ingelheim symposium had all been sponsored to attend the ECNP meeting by the two companies and the speakers had been chosen by the companies. The titles of the presentations had been mutually agreed and Lilly and Boehringer Ingelheim had reviewed the final papers to ensure compliance with the Code. The concept for the supplement was derived by Lilly and Boehringer Ingelheim and the companies paid for its production and distribution. The companies had certified the material in accordance with the Code.

The Panel considered that Lilly and Boehringer Ingelheim were wholly responsible for their meeting and thus for any output from it. There was no strictly arm's length arrangement. The supplement contained four papers of which the first referred to duloxotine and the third to olanzapine.

The Panel considered that the material at issue was not a supplement 'sponsored by Eli Lilly and Boehringer Ingelheim' as stated on the front cover but a paid for insert detailing the proceedings of a company meeting which had promoted Cymbalta and Zyprexa. In their response the companies had described the meeting as promotional and referred to the document as a promotional item. The Panel considered that the sponsorship statement disguised the promotional nature of the material. The reference to the UK Psychiatry Forum added to the misleading impression of a wholly independent meeting report. It was not stated that the 2008 meeting of the UK Psychiatric Forum was, in effect, a closed meeting run by Lilly and Boehringer Ingelheim. In that regard the forum had no recognised national standing. The Panel considered that the material was disguised promotion as alleged. A breach of the Code was ruled.

The Panel noted that Cymbalta was indicated, *inter alia*, for the treatment of major depressive episodes and the companies' submission that atypical depression was a sub-type of major depressive disorder. The Panel considered that the insert thus did not promote Cymbalta for an unlicensed indication as alleged. No breach was ruled.

The Panel considered that presenting the output of a company run meeting as an independent supplement to a journal demonstrated apparent

poor knowledge of the requirements of the Code. Health professionals generally looked to medical journals as a source of independent information; where authors wrote on behalf of companies or as a result of the activities of pharmaceutical companies this must be made clear. In the Panel's view the majority of readers would have viewed the material at issue quite differently if they had known that it was the report of a promotional company meeting and that the UK Psychiatric Forum was, in fact, a small group of health professionals chosen by Lilly and Boehringer Ingelheim with the titles of the papers presented being mutually agreed. The Panel considered that the description and presentation of the insert was such as to reduce confidence in, and bring discredit upon the pharmaceutical industry. A breach of Clause 2 was ruled.

An anonymous doctor complained about a journal supplement distributed with volume 13, issue 1 2009 of Progress in Neurology and Psychiatry. The material at issue was described as a report from the 2008 UK Psychiatry Forum and as 'A Progress supplement sponsored by Eli Lilly and Boehringer Ingelheim'. Prescribing information for Cymbalta (duloxetine) appeared on the back cover and that for Zyprexa (olanzapine) appeared on the inside back cover.

COMPLAINT

The complainant noted that the supplement had been produced to look exactly like the actual journal. There was only a small, non-prominent and easily missed statement at the bottom of the supplement indicating sponsorship by a pharmaceutical company.

On picking up the supplement it was misleading as it appeared that the UK Psychiatry Forum was a body of some significant standing. The forum was an independent body but the complainant was not aware that it held any major impact in psychiatry academia or otherwise. It was certainly not of any regulatory significance or responsible for any nationally implemented guidelines. A junior doctor reading the report might be misled as to its significance.

The complainant stated that the actual event that was reported was questionable. The complainant was in Barcelona last year and heard all the authors speak at a Lilly promotional meeting in exactly the same order, giving exactly the same talks that were repeated in this report. The complainant noted that this entire meeting was reported to have taken place as a forum of this body on the same dates and at the same place as the European College of Neuropsychopharmacology (ECNP) Lilly promotional symposium for UK doctors. The complainant alleged that the supplement thus misreported the actual event. The material was misleading and appeared to be disguised promotion.

The complainant noted that the supplement detailed a case of atypical depression. According to the Cymbalta summary of product characteristics (SPC), it was not licensed for atypical depression. This was off-licence promotion in breach of Clause 3.2.

The complainant alleged that the supplement, in its entirety, was misleading and it was disappointing that the journal concerned had allowed it to be printed. Furthermore, such actions brought disrepute to an industry at a time when transparency in the NHS and industry was vital to ensure trusting mutual collaborative practice that benefitted the service provided to patients.

The complainant alleged breaches of Clauses 2, 3.2 and 12.1 of the Code.

RESPONSE

Lilly and Boehringer Ingelheim stated that the supplement was a promotional item that was clearly labelled to indicate that it had been sponsored by the two companies. This was stated prominently on the front cover: 'A Progress supplement sponsored by Eli Lilly and Boehringer Ingelheim. Abbreviated prescribing information can be found on pages 11 and 12'; an additional sponsorship statement appeared underneath the abbreviated prescribing information on the back cover. Lilly and Boehringer Ingelheim therefore did not consider that the complainant's contention of 'a small non-prominent and easily missed statement at the bottom of the supplement indicating sponsorship by a pharmaceutical company' was correct. The companies presumed this allegation referred only to the final page of the item, where the font size under the prescribing information was smaller; they did not consider that readers were likely to miss the statement on the front cover.

The cover and layout of the supplement was consistent with the journal as stated by the complainant. This, however, was common practice with most journal supplements and was not unique to this one. Pharmaceutical companies commonly sponsored supplements and in the UK the British Journal of Psychiatry and the Journal of Psychopharmacology (amongst many others) regularly produced supplements that were included within the mailing of issues of the journal.

With regard to the allegation that the term UK Psychiatry Forum was misleading and that junior doctors might be misled as to its significance, the companies noted that the supplement was titled 'A report from the 2008 UK Psychiatry Forum' on the front cover. In the introduction it was stated that the meeting of the forum was held in Barcelona on 29 August 2008. The forum thus referred to the gathering of a group of health professionals who attended this meeting. The use of 'forum' was meant to convey the essence of the term meeting rather than ascribe any importance to the group of clinicians who took part in the forum. No statement

was made relating to the importance or significance of this group in any manner. The speakers at the meeting were, however, described as 'an eminent faculty' and were named in the introduction. The chairman concluded his introduction with the hope the reader found the report interesting and useful in their clinical practice. The companies did not consider that any of the above would lead the reader to conclude that the UK Psychiatry Forum was a body of some significant standing as suggested by the complainant. No statement was made that could lead the reader to conclude that the forum had any regulatory significance or was responsible for any nationally implemented guidelines.

The companies noted the complainant's statement that the actual event that was reported was questionable. The introduction section on page 2 described the event as a 'symposium' from which the papers in the supplement were summarised. Details of the 'eminent faculty' were also given in the introduction and included some highly respected clinicians and academics. The complainant was correct in his/her assertion that this symposium was an Eli Lilly/Boehringer Ingelheim promotional meeting in Barcelona held during the 2008 ECNP congress. Although further details of the event might have aided greater clarity the companies did not accept that this amounted to a breach of Clause 12.1. The supplement was clearly labelled as being sponsored.

The companies noted the complainant's allegation of a breach of Clause 3.2. In one of a series of cases of patients with depression and anxiety, the author stated that the patient was likely to have had 'atypical major depressive disorder'. Lilly and Boehringer Ingelheim denied that any off-licence promotion had taken place. Cymbalta was licensed for major depressive episodes as was stated in the prescribing information. The Diseases and Statistics Manual of Mental Disorders IV Text Revision (DSM-IV-TR), a widely used manual for diagnosing mental disorders, defined atypical depression as a subtype of depression or dysthmia, characterised by atypical features. In addition, in the World Health Organisation's International Classification of Diseases (ICD-10) atypical major depressive disorder would fall in the category F32 (depressive episode) or F33 (recurrent depressive disorder). The companies contended that these diagnostic manuals made clear that atypical depression was a subtype of major depressive disorder. The item clearly stated a diagnosis of 'atypical major depressive disorder' which was consistent with the Cymbalta SPC; Cymbalta was licensed for all forms of major depressive disorder.

The companies disagreed with the complainant's allegation that the supplement was misleading in its entirety; no part of the supplement was misleading. It was clearly stated to be an eminent faculty report which contained relevant clinical data in a number of psychiatric illnesses, data which the companies hoped might be useful to clinicians.

Lilly and Boehringer Ingelheim did not agree that the sponsorship of the supplement, its content or dissemination was likely to bring disrepute to the industry.

In summary, the companies did not consider that there was substance to the complainant's allegations of breaches of Clauses 2, 3.2 or 12.1.

Lilly and Boehringer Ingelheim provided copies of the invitation, agenda and presentations given at the meeting in Barcelona. Ninety clinicians sponsored by Lilly and Boehringer Ingelheim to attend the ECNP congress in Barcelona attended the symposium and this was the group that was referred to as the UK Psychiatric Forum participants. There was no obligation to attend the UK psychiatric meeting, however the invitees were given an agenda that allowed them to attend this meeting on 29 August that took place in a closed meeting room in their hotel in Barcelona. The faculty to deliver presentations was brought together by Lilly/Boehringer Ingelheim to present lectures to the participants on the basis of their scientific and academic abilities, with each lecture being of 20 minutes. The majority of the faculty were internationally published authors. The supplement concept was derived by Lilly/Boehringer Ingelheim and a fee was paid to the publisher of Progress in Neurology and Psychiatry for the production and dissemination of the supplement. A medical writer attended, as reported in the supplement, to draft the first versions of the papers based on the presentations. The content of the presentations was not influenced by Lilly/Boehringer Ingelheim, although the titles for the talks were mutually agreed to reflect the relevant expertise of the speakers and clinicians. The final versions of the papers were completed and approved by the authors and at this stage the sponsoring companies viewed the papers to ensure compliance with the Code but not to exert any other editorial control. The final promotional item was reviewed and certified in accordance with the Code prior to distribution.

PANEL RULING

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The Panel noted that the material in question provided the proceedings of a promotional symposium run by Lilly and Boehringer Ingelheim at the time of the ECNP congress, in the form of a journal supplement. The 90 delegates to the Lilly and Boehringer Ingelheim symposium had all been sponsored to attend the ECNP meeting by the two companies and the speakers had been chosen by the companies. The titles of the presentations had been mutually agreed and Lilly and Boehringer Ingelheim had reviewed the final papers to ensure compliance with the Code. The concept for the supplement was derived by Lilly and Boehringer Ingelheim and the companies paid for its production and distribution. The companies had certified the material in accordance with the Code.

The Panel considered that Lilly and Boehringer Ingelheim were wholly responsible for their meeting and thus for any output from it. There was no strictly arm's length arrangement. The supplement contained four papers: 'Depression and comorbid anxiety: case histories', 'The clinical challenge of bipolar mixed states', 'Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder' and 'Does patient choice improve long-term outcomes?'. The first paper referred to duloxotine and the third to olanzapine.

The Panel considered that the material at issue was not a supplement 'sponsored by Eli Lilly and Boehringer Ingelheim' as stated on the front cover but a paid for insert detailing the proceedings of a company meeting which had promoted Cymbalta and Zyprexa. In their response the companies had described the meeting as promotional and referred to the document as a promotional item. The Panel considered that the sponsorship statement disguised the promotional nature of the material. The reference to the UK Psychiatry Forum added to the misleading impression of a wholly independent meeting report. It was not stated that the 2008 meeting of the UK Psychiatric Forum was, in effect, a closed meeting run by Lilly and Boehringer Ingelheim. In that regard the forum had no recognised national standing. The Panel considered that the material was disguised promotion as alleged. A breach of Clause 12.1 was ruled.

The Panel noted that Cymbalta was indicated, *inter alia*, for the treatment of major depressive episodes. In the paper on 'Depression and comorbid anxiety; case histories' the first case history presented was of a patient with atypical major depressive disorder. The Panel noted the companies' submission that this was a sub-type of major depressive disorder. The Panel considered that the insert thus did not promote Cymbalta for an unlicensed indication as alleged. No breach of Clause 3.2 was ruled.

The Panel considered that presenting the output of a Lilly and Boehringer Ingelheim run meeting as an independent supplement to a journal demonstrated apparent poor knowledge of the requirements of the Code. Health professionals generally looked to medical journals as a source of independent information; where authors wrote on behalf of companies or as a result of the activities of pharmaceutical companies this must be made clear. In the Panel's view the majority of readers would have viewed the material at issue quite differently if they had known that it was the report of a promotional company meeting and that the UK Psychiatric Forum was, in fact, a small group of health professionals chosen by Lilly and Boehringer Ingelheim with the titles of the papers presented being mutually agreed. The Panel considered that the description and presentation of the insert was such as to reduce confidence in, and bring discredit upon the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received		**11 March 2009**
Cases completed	**AUTH/2213/3/09**	**20 April 2009**
	AUTH/2214/3/09	**14 April 2009**

CODE OF PRACTICE REVIEW – MAY 2009

Cases in which a breach of the Code was ruled are indexed in **bold type.**

2164/9/08	**Merck Sharp & Dohme v Takeda**	**Actos and Competact journal advertisement**	**Breach Clause 3.2 Two breaches Clause 7.2**	**Appeal by respondent**	**Page 3**
2177/10/08	**Allergan v Merz Pharma**	**Xeomin leavepiece**	**Two breaches Clause 7.2 Breaches Clauses 7.8 and 7.10**	**Appeal by respondent**	**Page 18**
2182/11/08	Genus v Stiefel Laboratories	Alleged inappropriate rebate	No breach	No appeal	Page 31
2183/11/08	**Merz Pharma v Allergan**	**Botox representative activity**	**Breaches Clauses 7.2, 7.3, 7.10, 9.1 and 15.9**	**No appeal**	**Page 33**
2189/12/08	General Practitioner v ProStrakan	Provision of a service	No breach	No appeal	Page 38
2190/12/08 and 2194/12/08	Anonymous Health Professionals v AstraZeneca	Conduct of representative	No breach	No appeal	Page 42
2191/12/08	**Novartis v Roche**	**Bondronat detail aid**	**Six breaches Clause 7.2 Five breaches Clause 7.3 Breach Clause 7.4 Two breaches Clause 7.8 Breaches Clauses 7.10 and 8.1**	**No appeal**	**Page 46**
2192/12/08	**Voluntary Admission by Pfizer**	**Lipitor journal advertisement**	**Breach Clause 25**	**Appeal by respondent**	**Page 57**
2193/12/08	Anonymous v Merck Serono	Promotion of Pergoveris	No breach	No appeal	Page 62
2195/12/08	**General Practitioners v Otsuka**	**Conduct of representative**	**Breaches Clauses 8.2, 9.1 and 15.2**	**No appeal**	**Page 65**
2196/1/09	**Anonymous Oncologist v AstraZeneca**	**Arimidex promotional aid**	**Breaches Clauses 9.1, 18.1 and 18.2**	**No appeal**	**Page 68**
2197/1/09	**Sanofi Pasteur MSD v MASTA**	**Epaxal promotional email**	**Breaches Clauses 9.1, 15.1 and 15.2**	**No appeal**	**Page 71**
2199/1/09	**Novartis v Roche**	**Bondronat leavepiece**	**Six breaches Clause 7.2 Three breaches Clause 7.3 Breaches Clauses 7.4, 7.8, 7.10 and 9.1**	**No appeal**	**Page 74**

2201/1/09	**AstraZeneca v Novartis**	**Femara press release**	**Breaches Clauses 2 and 9.1 Four breaches Clause 22.2**	**No appeal**	**Page 83**
2202/1/09	**Lilly v Novo Nordisk**	**Diabetes supplement in The Times**	**Breaches Clauses 2, 3.1, 9.1, 22.1 and 22.2**	**No appeal**	**Page 89**
2203/1/09	**Johnson & Johnson v Pfizer**	**Champix journal advertisement**	**Breach Clause 7.2**	**No appeal**	**Page 92**
2204/1/09	**Medicines and Healthcare Products Regulatory Agency v AstraZeneca**	**Zoladex journal advertisement**	**Breach Clause 9.5**	**No appeal**	**Page 97**
2206/2/09	**Voluntary admission by AstraZeneca**	**Crestor email**	**Breach Clause 3.2 Two breaches Clause 4.1 Breach Clause 7.2 Three breaches Clause 7.4 Breach Clause 7.9 Three breaches Clause 7.10 Breach Clause 9.1 Two breaches Clause 14.1**	**No appeal**	**Page 98**
2207/2/09	**Cephalon v Prostrakan**	**Promotion of Abstral**	**Breach Clause 3.2**	**No appeal**	**Page 102**
2208/2/09	Health Professional v Gilead Sciences	Unsolicited email	No breach	No appeal	Page 105
2210/3/09	Anonymous v AstraZeneca	Conduct of representative	No breach	No appeal	Page 107
2211/3/09	**General Practitioner v Boehringer Ingelheim**	**Micardis and Micardis Plus journal advertisement**	**Breaches Clauses 3.2, 7.2 7.4 and 7.10**	**No appeal**	**Page 112**
2213/3/09 and 2214/3/09	**Anonymous Doctor v Lilly and Boehringer Ingelheim**	**Sponsored supplement**	**Breaches Clauses 2 and 12.1**	**No appeal**	**Page 115**

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.