PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 30 NOVEMBER 2000

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.

Revision of Code and Constitution and Procedure postponed

In July, proposals for amendment of the Code of Practice for the Pharmaceutical Industry and the Constitution and Procedure for the Prescription Medicines Code of Practice Authority were circulated for comment to the chief executives of ABPI member companies and those non-member companies which had agreed to comply with the Code of Practice and accept the jurisdiction of the Code of Practice Authority. The British Medical Association, the Medicines Control Agency and the Royal Pharmaceutical Society of Great Britain were also consulted. The Authority is grateful to all those who submitted comments.

The ABPI Board of Management had agreed that the proposals could be sent out for consultation but had not itself as yet considered them at that time.

The proposed changes to the Code itself arose from problems of interpretation which had occurred, from recommendations of the Code of Practice Appeal Board, from recommendations of working parties and from external factors. The proposed changes to the Constitution and Procedure arose partly from problems which had emerged in its operation and partly from external factors.

It had been hoped that it would be possible to put proposals for amendment before member companies at the ABPI Half-Yearly General Meeting in October with a view to a new Code taking effect at the beginning of 2001.

In the event, however, because of the number of comments received and the shortage of time, the ABPI Board of Management decided to postpone putting proposals before member companies until the ABPI Annual General Meeting in April 2001. If then agreed, a revised Code and Constitution and Procedure will come into effect on 1 July 2001.

New Appeal Board Chairman

Mr Nicholas Browne QC has been appointed Chairman of the Code of Practice Appeal Board and is welcomed by the Authority. Mr Browne succeeds Mr James Hunt QC who is now a High Court Judge.

Since taking silk in 1995, Mr Browne has specialised in the criminal field, his cases involving murder, manslaughter, commercial fraud, particularly corporate defence work with international links, international drug trials and money laundering.

Mr Browne serves on the Professional Conduct Committee of the Bar Council, of which he is a former member, and sits for a total of about four weeks each year as a Recorder on the Midland and Oxford Circuit, trying both criminal and civil cases.

Advice on the application of the Code

Members of the Authority are willing to advise on the application and interpretation of the Code and their direct line telephone numbers are always given in the Code of Practice Review. They try to help enquirers and are usually able to do so.

They cannot, however, approve promotional material or novel methods of promotion and the decision as to whether or not to proceed is one for the company's signatories to take. If a complaint is subsequently received it will be dealt with in the usual way. It has to be borne in mind that the three members of the Authority, who also make up the Code of Practice Panel, do not have the last word on the application and interpretation of the Code as their rulings can be overturned by the Code of Practice Appeal Board.

If, as happened recently, a provider, or potential provider, of services to the industry implies that a novel form of promotion, or a novel way of approaching health professionals or hospitals, has the approval of the Authority, or of the ABPI itself, this is unlikely to be true and the Authority should be consulted before any reliance is placed upon what has been said.

CODE OF PRACTICE TRAINING

Training seminars on the Code of Practice, open to all comers, are run by the Code of Practice Authority on a regular basis at the Royal Society of Medicine in London.

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

Forthcoming Code of Practice seminar dates on which places remain available are:

Tuesday, 30 January

Tuesday, 27 February

Tuesday, 20 March

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 Jean Rollingson for details (020 7930 9677 extn 1443).

How to contact the Authority

Our address is:

Prescription Medicines
Code of Practice Authority
12 Whitehall
London SW1A 2DY

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7930 9677 extn 1473).

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.

GENERAL PRACTITIONER and SMITHKLINE BEECHAM v LUNDBECK

Antidepressant sampling study

A general practitioner complained about market research being carried out on behalf of Lundbeck by a market research company, alleging that it amounted to an inducement to prescribe Lundbeck's product Cipramil. The aim of the market research was to assess the value of sampling products for the treatment of depression. Doctors agreeing to take part in the market research were sent four sample packs of Cipramil, four patient questionnaires and one doctor questionnaire. Questionnaires were to be returned to the market research company which would send the doctor £50 of high street store vouchers. It appeared to the complainant that this was disguised promotion in that free samples of Cipramil were being supplied to secure further prescriptions together with a clear financial inducement to do so. The complainant noted that the samples were for one month but antidepressants needed to be prescribed for six months beyond the time to recovery. If patients had been put on these tablets, further Cipramil would have had to be prescribed to achieve adequate antidepressant activity. As a result of Lundbeck's activities doctors participating in this so called market research might be endangering their professional standing and Lundbeck was unacceptably lowering the standards of promotional methods for the pharmaceutical industry.

A similar complaint was made by SmithKline Beecham which also made a number of additional allegations relating to the activity in question and papers associated with it. It was alleged by SmithKline Beecham that Lundbeck was bringing the industry into disrepute.

The Panel noted that the only requirement in the Code relating to market research was that market research must not be disguised promotion. The supplementary information gave more guidance and referred to the Guidelines on Pharmaceutical Market Research Practice produced by the British Pharmaceutical Market Research Group and the ABPI.

It was clear from the documentation that participants were expected to use the Cipramil samples. Only one month's supply was provided for each of four patients. The Cipramil summary of product characteristics stated that in depression 'A treatment period of at least six months is usually necessary to provide adequate maintenance against the potential for relapse'. In the Panel's view it was likely that once a patient had been given the sample of Cipramil, treatment with that medicine would be continued for some months at least. The Panel noted Lundbeck's submission that the objectives of the study were 'to evaluate the value of samples of psychoactive medicines and to obtain data regarding the management of depression in general practice.' The Panel queried whether the actual provision of samples of any medicine were required in order to meet these objectives.

The Panel questioned whether the study was being conducted in an attempt to answer valid scientific questions. Given the stated purpose of the study, the Panel found it difficult to accept the need for doctors to start four patients on Cipramil therapy. Having started patients on Cipramil, therapy would have to be continued and it was highly likely that this would be Cipramil. The Panel decided that the study was unacceptable as the arrangements were such that in effect it amounted to paying doctors to prescribe Cipramil. The Panel considered that the study constituted disguised promotion of Cipramil and accordingly ruled a breach of the Code. As the study was considered to be disguised promotion, it followed that payments for participation were inappropriate and a breach was also ruled in that regard. Overall the Panel considered that high standards had not been maintained and that the study brought discredit upon the pharmaceutical industry. Breaches of Clauses 2 and 9.1 were ruled. It was also decided to report Lundbeck to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

These rulings and the report to the Appeal Board applied to both of the cases arising from the two complaints about the matter. In addition, the Panel considered the additional allegations made by SmithKline Beecham.

A breach of the Code was ruled because prescribing information included on a letter was not clear and legible as required. As the study was considered to be disguised promotion, use of the telephone to solicit participation in it, without the prior permission of the recipients, was inappropriate and a breach of the Code was ruled. Similarly, failure to declare Lundbeck's sponsorship of promotional material was ruled in breach. No breach was ruled in relation to the fact that samples had been provided nor in relation to an allegation that sample requests should not be solicited. No breach was also ruled in relation to allegations concerning gifts of mugs and coasters and the sending of a newsletter.

Lundbeck appealed the ruling of a breach of Clause 2 whilst accepting other rulings of breaches of the Code. The Appeal Board noted that Lundbeck had changed its procedures as a result of these cases. The company had apologised and confirmed that action had been taken to halt the study following receipt of the Panel's decision in the first case. The Appeal Board accepted that data evaluating the provision of samples by the pharmaceutical industry might be of interest but the design and arrangements for the study in question would not have answered those questions. The Appeal Board was extremely concerned about the study which in effect amounted to paying doctors to prescribe Cipramil. The Appeal Board considered that the study brought discredit upon and reduced confidence in the pharmaceutical industry and

upheld the Panel's ruling of a breach of Clause 2 of the Code.

The Appeal Board then considered the report made by the Panel under Paragraph 8.2 of the Constitution and Procedure. The Appeal Board decided that, in accordance with Paragraph 10.4 of the Constitution and Procedure, Lundbeck should be required to undergo an audit of its procedures relating to the Code of Practice. This would be carried out by the Authority. The Appeal Board would decide whether any further action was required once it had received the report on the audit.

When the Appeal Board considered the report on the audit, which had taken place on 6 July, it also had before it a letter from Lundbeck responding to recommendations made in the report and undertaking to implement them. On that basis, the Appeal Board decided that the matter would be closed.

Case AUTH/986/3/00

A general practitioner complained about market research which was conducted on behalf of Lundbeck Ltd by an independent market research company. The aim of the market research was to assess the value of sampling products for the treatment of depression. Doctors agreeing to take part in the market research were sent four sample packs of Cipramil, four 'patient questionnaires' and one 'doctor questionnaire'. Questionnaires were to be returned to the market research company which would then send the doctor £50 of high street store vouchers.

COMPLAINT

The complainant alleged that the market research undertaken by Lundbeck was an inducement to doctors to use its products.

The complainant stated that she was initially telephoned by the market research company which told her that it was conducting market research on antidepressants and that if she was prepared to answer some questionnaires it would pay her £50 in store vouchers. The complainant stated that as she had previously done market research exercises she thought this seemed reasonable and agreed to participate. The complainant was then sent a letter from the company which detailed the way the market research worked, and it was at this point that her suspicions were first raised. The market research comprised the complainant requesting four sample packs of Cipramil and once she had received these and associated questionnaires she was encouraged to put four of her patients on Cipramil, complete the questionnaires, return them to the market research company and she would then be paid £50. It appeared to the complainant that this was clearly disguised promotion and that free samples of Cipramil were being supplied to secure further prescriptions together with a clear financial inducement to do so. The complainant noted that the samples were for one month but antidepressants needed to be prescribed for six months beyond the time to recovery. The complainant stated that if she had put patients on these tablets she would then have had to prescribe further Cipramil to achieve adequate antidepressant activity.

The complainant was extremely concerned that as a result of Lundbeck's activities doctors participating in this so called market research might be endangering their professional standing and that Lundbeck by its activities was unacceptably lowering the standards of promotional methods for the pharmaceutical industry.

RESPONSE

Lundbeck stated that the market research company was working on its behalf to evaluate the usefulness of samples of antidepressants. Lundbeck was aware that sampling was widely practised; however the impact had not been systematically evaluated. Lundbeck stated that the objectives of the study were to evaluate the value of samples of psychoactive medicines and to obtain data regarding the management of depression in general practice.

There were two forms that doctors were asked to complete. A 'patient' evaluation to be completed after a consultation and follow up of an individual patient. A 'doctor' form which evaluated the clinician's perspective of the supply of samples and their suitability (or not) for use with patients. Since the forms were extensive, it was appropriate to offer reimbursement to clinicians who completed them. There was no linkage of reimbursement to the use of samples; Lundbeck had made this clear to the market research company when the evaluation was set up and had asked it to make this point clear to participants.

Lundbeck stated that initial contact was via a letter but it understood that the market research company had made telephone contact with 545 doctors as their forms were not returned and the company considered them likely participants for market research. Where practitioners indicated an interest in participating a follow-up letter was sent. This letter identified Lundbeck as the sponsor and Cipramil as the product. Copies of the two letters were provided.

The follow-up letter explained to participants that they would receive £50 in store vouchers for their time in completing questionnaires and that they must complete a sample request form so that accurate records could be kept of who received the samples. Lundbeck noted that the letter stated that reimbursement would be made upon return of the questionnaires; this statement was unqualified as the company appreciated that some would be returned incomplete. Lundbeck had indicated to the market research company that all returned documents would be evaluated whether complete or not. Lundbeck noted that in the introductory remarks in the follow-up letter, received once a doctor had agreed to take part in the study, the market research company requested 'fullest' responses to the questionnaires but there was no mandate for total completion. At no point in any of the documentation was there any implicit or overt requirement for doctors to prescribe Cipramil. A copy of the letter which accompanied the samples was provided.

Lundbeck agreed with the complainant that the samples of Cipramil were only enough for a month's treatment and that treatment of depressed patients should continue for a period of time after clinical response. However, it was Lundbeck's contention that at no stage within communications with interested participants was there any statement about either treatment periods or a requirement to prescribe Cipramil. As indicated earlier, sampling was a widespread activity but limited objective data existed as to the impact in clinical practice.

Lundbeck absolutely refuted the allegation that this activity was disguised promotion as alleged by the complainant. The market research company was a member of the British Pharmaceutical Market Research Group. As such, it was as aware as Lundbeck of the requirements of the Code and would not knowingly participate in a disguised promotional activity.

Lundbeck submitted that it had complied with the requirements of Clause 17. The packs of Cipramil were only issued after a signed sample request had been received and a record had been kept. The pack size was appropriate and labelled as per the requirements of Clauses 17.4, 17.5, 17.7 and 17.9.

Since the forms were extensive and the participants had to spend time completing them, it was entirely appropriate to offer a modest recompense for this. A fee of £10 per form was not excessive and appropriate for the time involved. The market research company was thus acting properly in offering these store vouchers for the completion and return of forms. There were no restrictions or conditions regarding reimbursement. Lundbeck emphatically denied that the vouchers were an inducement to prescribe Cipramil.

There had been no issuance of an inappropriate gift or inducement which would contravene Clause 18. The market research company was issuing vouchers to participants without any restrictions or conditions for their time in completing questionnaires.

With regard to Clause 9.1 of the Code, Lundbeck stated that it held the medical profession in high regard and had maintained high standards throughout. Lundbeck stated that it had enquired of the market research company as to any complaints that it had received following its mailings. Replies expressing interest had been received from 416 doctors. Following the second letter 315 had indicated willingness to participate, 91 had declined. No complaints had been received either by the market research company or by Lundbeck following the mailings.

Lundbeck submitted that it had followed the spirit of the Code. The company further maintained that it had not breached the clauses of the Code identified and therefore it was not in breach of Clause 2.

PANEL RULING

The Panel noted that the only requirement in the Code relating to market research was Clause 10.2. This stated that market research and other studies etc must not be disguised promotion. The supplementary information gave more guidance and referred to the Guidelines on Pharmaceutical Market Research Practice produced by the British Pharmaceutical Market Research Group and the ABPI.

The Panel noted that doctors were invited to participate in the study via a letter sent to them by the market research company. The letter was headed 'Antidepressant Sampling Study' and gave brief details of the work that would be involved. The letter stated that the study concerned the use of sample products for the treatment of depression. General practitioners were to be invited to participate to determine how useful the sampling service was and how GPs and patients benefited from it. The letter stated that participants would be supplied with product samples for four patients and would be asked to fill in questionnaires regarding the use of the product. Following receipt of the completed questionnaire doctors would be offered a choice of vouchers for W H Smith, Marks & Spencer or Boots to the value of £50. It was stated that all comments regarding patients and their use of the sampled products would be treated in absolute confidence. The letter made no mention that the study was being undertaken on behalf of a pharmaceutical company. The second letter sent by the market research company incorporated the sample request form. The letter stated that it was being sent so that 'you may request the antidepressant samples for your use in this research.' The sample request form stated 'Please provide me with four sample packs of Cipramil … in order for me to take part in this research'. A space was left for a signature and a date. Beneath this section the prescribing information for Cipramil was given. The third letter which accompanied the samples of Cipramil gave detailed instructions for completion of the research. The first step was to 'hand one sample pack of Cipramil to each of four patients of your choice'. Once the sample pack had been handed out Section 1 of the patient questionnaire was to be completed (sixteen questions); Section 2 (five questions) was to be completed when the patient returned to the surgery following the use of the sample pack. Part one of the questionnaire asked questions about the patient and their condition generally while part two began 'As a result of using the sample …'. The questions assumed that the patient had been switched to Cipramil or that treatment was initiated with Cipramil.

Once the patient questionnaires were completed participants were asked to complete a doctor questionnaire. This consisted of fifteen questions. The first question related to the use of antidepressants in the last three months. The next few questions related to use of antidepressants samples generally, such as what samples had the GP been given/used?, When and where did they use antidepressant samples?, What advantages/disadvantages did such samples have for the patient/doctor? etc. This was followed by questions about the treatment of patients with depression.

The Panel considered that from the documentation it was clear that participants were expected to use the Cipramil samples. Only one month's supply was provided for each of four patients. The Panel noted

that the Cipramil summary of product characteristics (SPC) stated that in depression 'A treatment period of at least six months is usually necessary to provide adequate maintenance against the potential for relapse' (ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000). In the Panel's view it was likely that once a patient had been given the sample of Cipramil, treatment with that medicine would be continued for some months at least.

The Panel noted Lundbeck's submission that the objectives of the study were 'to evaluate the value of samples of psychoactive medicines and to obtain data regarding the management of depression in general practice.' The Panel queried whether the actual provision of samples of any medicine were required in order to meet these objectives.

The Panel questioned whether the study was being conducted in an attempt to answer valid scientific questions. Given the stated purpose of the study, the Panel found it difficult to accept the need for doctors to start four patients on Cipramil therapy. Having started patients on Cipramil, therapy would have to be continued for some months at least and it was highly likely that this would be Cipramil. The Panel decided that the study was unacceptable as the arrangements were such that in effect it amounted to paying doctors to prescribe Cipramil. The Panel considered that the study constituted disguised promotion of Cipramil. The Panel therefore ruled a breach of Clause 10.2 of the Code. As the study was considered to be disguised promotion it followed that payments for participation were inappropriate and a breach of Clause 18.1 was ruled in this regard.

Overall the Panel considered that high standards had not been maintained and that the study brought discredit upon the pharmaceutical industry. Breaches of Clauses 9.1 and 2 were ruled. It was also decided to report Lundbeck to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Panel noted that in order to obtain the samples of Cipramil participants had to sign and date a sample request form. The samples supplied were 4 x 28 Cipramil 20mg. These packs were no larger than the smallest presentation of Cipramil 20mg on the market. The samples were marked 'Free medical sample not for resale'. No breach of Clauses 17.3, 17.4 and 17.5 was ruled. The Panel made no ruling with regard to Clause 17.9 of the Code as it had insufficient information to make a decision and in any case the issue was not the subject of the complaint. Clause 17.7 of the Code dealt with the distribution of samples by representatives and was not relevant to this case.

APPEAL BY LUNDBECK

Lundbeck stated that as well as many other pharmaceutical companies, it supplied a large amount of samples to the medical profession and its aim with this market research was to genuinely identify the benefit and use of samples by GPs. The market research was done by an independent party in line with market research code of practice rules and it had never been Lundbeck's intention to elicit prescriptions for Cipramil. Lundbeck therefore contended the ruling of a breach of Clause 2 and referred this to the Appeal Board for its consideration.

Case AUTH/990/3/00

COMPLAINT

SmithKline Beecham Pharmaceuticals was concerned that, as a consequence of a market research initiative being conducted on behalf of Lundbeck Ltd, participating doctors might be endangering their professional standing and the company was unacceptably lowering the standards of promotional methods for the pharmaceutical industry.

SmithKline Beecham stated that individual general practitioners were being telephoned by a market research company. The GP was informed that the market research company was conducting market research in antidepressants and the GP was then informed that if they filled in some questionnaires they would be paid £50 in store vouchers. If they agreed on the telephone that they were interested in participating in this activity, they were then sent a letter from the market research company which detailed the way the market research was to be structured. SmithKline Beecham provided a copy of that letter which it stated essentially appeared to be a sample request form for Cipramil tablets.

SmithKline Beecham stated that once a written request for sample packs of Cipramil had been received, the GP was then sent 4 x 28 days' supply of Cipramil tablets with an individual patient questionnaire and a GP questionnaire, copies of which were provided. Having dispensed these packs to individual patients the patient was encouraged to complete a questionnaire at the end of the month and likewise the GP. The GP was subsequently sent £50 in store vouchers. It would appear that as a follow up to this activity the GP was sent unsolicited promotional material in the form of a depression club mailing and a promotional mug and coaster. A copy of the mailing was provided.

SmithKline Beecham stated that it had written to Lundbeck detailing its concerns regarding this activity and had unfortunately received unsatisfactory responses to each of the issues raised. Nor had Lundbeck arranged for this dubious activity to be ceased.

SmithKline Beecham alleged that a number of clauses of the Code had been breached.

- Clause 4.1: the provision of prescribing information in the sample request letter from the market research company was neither clear or legible in view of the tiny print size and extremely long line length. The letter 'x' in lower case was less than 1mm in height and the lines were well in excess of 100 characters in length. This was a clear breach of Clause 4.1.

- Clause 9.8: the use of the telephone to invite doctors to participate in the market research was unsolicited promotion in view of the promotional nature of the market research towards Cipramil tablets.

SmithKline Beecham stated that it had not been reassured that this activity was not promotional and considered that Lundbeck was providing a

prescribing inducement under the guise of market research.

- Clause 9.9: the requirement to declare sponsorship on all materials published by a pharmaceutical company had clearly not been met.

In view of this activity, which was a prescribing inducement under the guise of market research, this clearly was promotional for Cipramil and therefore not to have included any statements about company sponsorship in the initial letter was a breach of Clause 9.9.

- Clause 10.2: given that the market research involved the use of free samples of Cipramil tablets and that follow up on completion of the questionnaire was a Cipramil mug and a Lundbeck Newsletter, the market research was a form of disguised promotion rather than a *bona fide* attempt at researching antidepressant use in a non-promotional way. Moreover, the content of the questionnaires merely provided Lundbeck with important marketing intelligence on potential new customers and further supported this complaint.

SmithKline Beecham stated that if this promotional material follow up were just an inadvertent coincidence (which the company would dispute), then Lundbeck was in further breach of Clause 18.1, in view of the fact that it had sent unsolicited gifts in the post to GPs. SmithKline Beecham would also contend that there had been a further breach of Clause 18.2 in view of the fact that table mats were noted to be in breach and the company therefore contended that a coaster was also logically therefore in breach of Clause 18.2.

- Clause 17.1: the provision of samples for antidepressants was by nature promotional since depressed patients should receive treatment for at least six months, given the chronic nature of the disease. The provision of a free 28 day sample pack of Cipramil by Lundbeck for administration to patients was therefore likely to result in further prescriptions to cover subsequent months of treatment. The use of samples for antidepressants was thus an unethical means of gaining sales.

- Clause 17.3: the provision of samples should be unsolicited by pharmaceutical companies. In this case, although a sample request was required to be signed by a doctor before samples were provided by Lundbeck, the invitation to participate in the market research and hence receive the samples was solicited by Lundbeck via the telephone.

- Clause 18.1: the provision of £50 store vouchers to doctors who were participating in the market research was clearly an inducement for the supply, prescription and administration of Cipramil tablets. In addition the acceptance of the store vouchers by doctors was against the rules of 'Good medical practice' from the General Medical Council.

- Clause 2: in view of the multiplicity and seriousness of the above breaches.

SmithKline Beecham stated that Lundbeck's activity was of major concern. There were numerous serious breaches of the Code. Lundbeck had failed to appreciate that this activity was bringing the industry into disrepute.

RESPONSE

Lundbeck stated at the outset that it wished to correct one misconception from SmithKline Beecham. There was no follow up mailing, in particular the Depression Club Newsletter was not associated with the activities of the market research company. The promotional mug and coaster were also not related to the activities of the market research company.

Lundbeck explained that the Depression Club Newsletter was sent to clinicians who had specifically requested it and was distributed by a medical mailing house. Additional copies were sent to recipients of Psychiatry Reviews who had requested regular copies of Lundbeck's newsletter. The copies were distributed by Lundbeck representatives or the mailing house in response to requests from doctors. There was, therefore, no link between the market research company and distribution of these items. Lundbeck stated that it had spoken to SmithKline Beecham which indicated that it would accept the company's word on this matter.

Referring to the specific alleged breaches of the Code, Lundbeck's response was as follows;

Clause 4.1. The typeface for the prescribing information had been confirmed by the printers to be '6 point' which was accepted as a minimum size for such printing. The line length did exceed 100 characters, which was an oversight on Lundbeck's part.

Clause 9.8. Since Lundbeck considered that the activities of the market research company were non-promotional, use of the telephone was not inappropriate in the circumstances. The market research company had indicated that there was some 'cold calling' but in the main to doctors who had previously participated in market research with it.

Lundbeck stated that it was not sure as to the appropriate response to SmithKline Beecham's opinion on its response as it fell outside the scope of the Code.

Clause 9.9. Whilst Lundbeck acknowledged its involvement with the market research company to conduct the market research, it did not agree that the initial mailing required an indication as to the sponsoring company. Later mailings clearly identified Lundbeck as the sponsor as the company needed to make clear to participants that it would be keeping a log of all samples despatched as required under Clause 17 of the Code. Letters and information forms relating to this research were provided.

Lundbeck stated that it did not intend to respond to an opinion held by SmithKline Beecham as a corollary to this alleged breach.

Clause 10.2.Lundbeck stated that this had already been covered above.

The Depression Club Newsletter was non-promotional and was distributed to clinicians who had requested it. It was not sent as a follow up to market research company's mailings, that company had and still had no knowledge of the recipients of this newsletter. The mug and coaster (not table mat) were either sent in response to a signed request from

a clinician or via the representatives. Lundbeck stated that should SmithKline Beecham provide details of alleged complainants it would be pleased to send the Authority their details from its mailing lists.

Since there was no link between the letter, mug and coasters and the market research company Lundbeck contended that there was no requirement to provide them to the Authority. The company was also at a loss as to the reason for SmithKline Beecham to contend that 'table mats are noted to be a breach'. The company had received no complaint from SmithKline Beecham or from the Authority about the Cipramil coasters (which were permissible promotional items) so the company contended again that there had been no breach of Clause 18.1.

Clause 17.1.The opinion of SmithKline Beecham that the provision of samples of antidepressants was by nature promotional was perplexing. The company received many sample requests from clinicians, and provided samples against such requests and would not regard its actions as promotional.

Lundbeck conceded that the treatment of depression was a matter for extended treatment to ensure clinical remission and to prevent relapse. As a company it had no reliable data as to the utility (or otherwise) of Cipramil samples, hence it decided to conduct the market research. Since the market share of new selective serotonin reuptake inhibitor (SSRI) prescriptions for Cipramil was the largest in the therapeutic group, Lundbeck refuted that its intention with this research was to generate new Cipramil prescriptions. Whether samples were used was an open question, the company asked the GPs if they used the samples and what was said to patients about them. Therefore 'The use of samples for antidepressants was thus an unethical means of gaining sales' was frankly preposterous.

Clause 17.3.Lundbeck agreed entirely that samples should be requested; the company regularly received such requests from doctors for Cipramil.

As indicated in the initial letter from the market research company, the research was into the use of samples. It therefore followed that a sample request must be completed by anyone wishing to participate in the market research. With only a few exceptions initial contact was by letter, not telephone, when the telephone was used the calls invited participants in market research, which was followed by the despatch of written information. It was Lundbeck's contention that these letters and calls were not solicitations to request samples by the market research company on its behalf.

Clause 18.1.Lundbeck noted that the Code prohibited the issuance of financial rewards for prescriptions. The letter from the market research company clearly indicated that the provision of the vouchers was to recompense participants for their time in providing information on the market research questionnaires. Lundbeck was well aware of the risk of doctors returning their forms with minimal data, the market research company would still provide reimbursement for the time of these clinicians too.

Clause 2. Lundbeck noted that SmithKline Beecham had endeavoured to show a causal link between the market research and the issuance of unsolicited promotional items. This allegation was entirely false.

There was no implicit or *de facto* inducement to prescribe Cipramil.

Reimbursement was for the time of clinicians not for prescriptions issued since none were sought.

Completion of sample request forms was in compliance with the Code.

The company acknowledged that the line length of the prescribing information exceeded the allowable character length under Clause 4.1 of the Code. This was an oversight on behalf of the company and would not be repeated.

In the light of the foregoing Lundbeck submitted that there had not been multiple and serious breaches of the Code in contravention of Clause 2.

PANEL RULING

The Panel noted that this complaint had much in common with Case AUTH/986/3/00 which related to the same matter.

The Panel considered that its rulings in the previous case (AUTH/986/3/00) of breaches of Clauses 9.1, 10.2, 18.1 and 2 also applied in this case (AUTH/990/3/00). It therefore followed that this case should also be reported to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Panel noted that there was an error in the complaint from SmithKline Beecham, the patient questionnaire was to be completed by the participating doctor and not by the patient as stated in the letter of complaint.

The Panel noted that SmithKline Beecham had made some allegations which were not made in the previous case. The second letter incorporating the sample request form also incorporated the Cipramil abbreviated prescribing information. The quality of the copies of the letter provided to the Panel was extremely poor which made the text difficult to read. However it appeared that the type size used was such that a lower case 'x' was less than 1mm in height; there were certainly far in excess of 100 characters per line. The Panel did not consider that the prescribing information had been provided in a clear and legible manner as required by Clause 4.1 of the Code. A breach of that clause was ruled.

The Panel noted that as the study was considered to be disguised promotion it followed that the use of the telephone to encourage participation in it, without the prior permission of the recipients, was inappropriate and a breach of Clause 9.8 was ruled. It also followed that the failure to declare sponsorship was a breach of Clause 9.9 and a breach of that clause was ruled.

The Panel noted with regard to the declaration of sponsorship on materials relating to medicines and their uses that the Code was inconsistent with the Guidelines on Pharmaceutical Market Research Practice. Clause 9.9 of the Code stated that all material relating to medicines and their uses which was sponsored by a pharmaceutical company must

clearly indicate that it had been sponsored by that company. This would include market research exercises. Section 4.2 of the Guidelines, however, stated that at first approach the name and address of the organisation carrying out the work had to be made available to the informant but that this did not mean that an agency was obliged to reveal the identity of its client. That was a matter for the contract between the client and the agency. A survey should not, however, imply that it was independent of the pharmaceutical industry if it was in fact commissioned by, or for, one or more particular companies. Thus the Code required the identity of the pharmaceutical company to be given while the Guidelines in effect recommended that, at minimum, market research should make it clear that a pharmaceutical company was involved. The Panel noted that this was the first time that this issue had arisen. In the Panel's view it was not unreasonable for the identity of the pharmaceutical company commissioning market research to be kept confidential provided that it was made clear that the study had been sponsored by a pharmaceutical company. This would be addressed on the next revision of the Code. It did not affect the ruling of a breach of Clause 9.9 of the Code in this case.

Clause 17.1 of the Code stated that samples might only be provided to health professionals and must not be provided to administrative staff. The Panel considered that it was acceptable to offer sample packs of Cipramil; there was no prohibition on the provision of samples of antidepressants. There was no evidence to suggest that the Cipramil samples had been offered to anyone other than a health professional. No breach of Clause 17.1 was ruled.

The Panel considered that its ruling in the previous case of no breach of Clause 17.3 also applied in this case. The Cipramil samples had been supplied in response to a signed and dated written request. The Panel did not accept SmithKline Beecham's view that sample requests should be unsolicited. There was nothing to prevent companies from asking health professionals if they wanted samples. There were requirements regarding obtaining a signed and dated request, plus others regarding pack size, numbers of packs and accountability of samples.

The Panel noted Lundbeck's submission that the distribution of the Depression Club Newsletter and the provision of the Cipramil mug and coaster were entirely separate from the antidepressant sampling study. In the Panel's view the promotional mailing was not linked to the antidepressant sampling study. SmithKline Beecham had not referred to a clause number in relation to this aspect of the complaint. The Panel decided therefore that it would be inappropriate for it to make a ruling. It was not unacceptable to send unsolicited promotional aids as alleged and no breach of Clause 18.1 of the Code was ruled in that regard. The Panel considered that mugs and coasters were acceptable gifts. The supplementary information to Clause 18.2 stated that table mats, not coasters, were unacceptable. The Panel noted that the complaint concerned the relevance of coasters and not their cost. The Panel did not know the unit cost of either the mugs or the coasters but it was unlikely that either would cost more than £5 plus VAT. Neither item was considered unacceptable and no breach of Clause 18.1 was ruled. It was not possible to breach Clause 18.2 which gave an exemption to the requirements of Clause 18.1.

The Panel noted that the only allegation about the newsletter was that it had formed part of the mailing to participants in the antidepressant sampling study. There was no complaint about the newsletter itself. The Panel did not accept Lundbeck's view that the newsletter was not promotional and requested that the company be so advised. It had been produced by Lundbeck and included a report from a scientific symposium, sponsored by the company, which had discussed the clinical use of Cipramil. An article on antidepressants and drug interactions contained claims for Cipramil with regard to its potential for such interactions and its use in the elderly. The back cover of the newsletter featured a Cipramil advertisement.

APPEAL BY LUNDBECK

Lundbeck stated that the project was initiated with entirely creditable intent. There was a genuine need to evaluate the practice of sampling by the pharmaceutical industry for the following reasons: sampling was extensively undertaken by the pharmaceutical industry in a wide range of therapy areas; little was known about how these samples were used; the definition and use of samples was relatively vague 'A sample is a small supply of a medicine provided to members of the health professions in order that they may familiarise themselves with it and acquire experience in dealing with it' (supplementary information to Clause 17); and there had been no previous evaluation of the circumstances associated with sample usage published in the scientific literature.

The project was implemented by an independent market research company on Lundbeck's behalf in line with the guidelines on pharmaceutical market research practice. On reflection, Lundbeck accepted that the design employed to address this question could have been different and the supervision of the market research company should have been better. However, Lundbeck could assure the Appeal Board that it was never its intention to bring discredit upon the pharmaceutical industry but to generate data to evaluate a poorly researched area of widespread interest to the industry.

Lundbeck had acted expeditiously to terminate the project as soon as it received the Panel's ruling and it asked that the finding of a breach of Clause 2 be reconsidered by the Appeal Board.

Cases AUTH/986/3/00 and AUTH/990/3/00

APPEAL BOARD RULING

The Appeal Board noted that Lundbeck had changed its procedures as a result of these cases. The company's representatives had apologised and confirmed that action had been taken to halt the study following receipt of the Panel's decision in the first case.

The Appeal Board accepted that data evaluating the provision of samples by the pharmaceutical industry might be of interest but the design and arrangements for the study in question would not have answered those questions. The Appeal Board was extremely concerned about the study which in effect amounted to paying doctors to prescribe Cipramil.

The Appeal Board considered that the study brought discredit upon and reduced confidence in the pharmaceutical industry and upheld the Panel's ruling of a breach of Clause 2 of the Code. The appeal in this regard was unsuccessful.

REPORT FROM THE PANEL TO THE APPEAL BOARD

The Appeal Board considered the report made by the Panel under Paragraph 8.2 of the Constitution and Procedure. The Appeal Board decided that, in accordance with Paragraph 10.4 of the Constitution and Procedure, Lundbeck should be required to undergo an audit of its procedures relating to the Code of Practice. This would be carried out by the Authority.

The Appeal Board would decide whether any further action was required once it had received the report on the audit.

When the Appeal Board considered the report on the audit, which had taken place on 6 July, it also had before it a letter from Lundbeck responding to recommendations made in the report and undertaking to implement them. On that basis, the Appeal Board decided that the matter would be closed.

Complaints received

Case AUTH/986/3/00	**7 March 2000**
Case AUTH/990/3/00	**24 March 2000**
Cases completed	**6 September 2000**

CASE AUTH/987/3/00

CONSULTANT PHYSICIAN v NAPP

Sponsorship of journal supplement on oxycodone

A consultant physician complained about a Therapeutic Advances supplement issued with the journal Prescriber which was entitled 'Oxycodone for pain malignancy and postoperative pain'. Four sections discussed the pharmacology of oxycodone, approaches to analgesia in malignancy, the place of oxycodone in the management of postoperative pain and pain in malignancy. There was also a GP's perspective of the product. Four independent authors had contributed to the supplement. The front cover stated that the publication was 'A Prescriber supplement supported through an educational grant from Napp Pharmaceuticals'. Napp marketed four formulations of oxycodone – Oxycontin tablets, Oxynorm capsules and Oxynorm liquid and concentrate. The complainant stated that the supplement appeared to represent, in all but name, an advertisement for oxycodone without any summary of product characteristics.

The Panel first had to decide whether the journal supplement was subject to the Code. The supplement had been sponsored by a company with a commercial interest in the medicine featured and was thus potentially subject to the Code. 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. The Panel noted that Napp's only involvement in the production of the supplement had been to provide financial sponsorship. The company had not chosen the authors and had had no editorial control. The complainant had received the supplement with the copy of Prescriber and not from the company or its representatives. In these circumstances the supplement did not have to include the prescribing information. The Panel ruled no breach of the Code in that regard. The Panel considered that the production of the journal and its distribution by Prescriber did not amount to disguised promotion and nor did it fail to maintain high standards. No breach of the Code was ruled in that regard.

Upon appeal by the complainant, the Appeal Board noted that Napp's involvement with the production of the supplement had now become clearer. Napp had made comments on the draft manuscripts, some of which had been accepted. The company had thus had some input into the articles. The Appeal Board noted that the supplement discussed the use of one medicine, oxycodone, in the management of pain of malignancy and postoperative pain. Each article contained a shaded box highlighting 'Key points' some of which, in the Appeal Board's view, could be considered to be claims for oxycodone. The Appeal Board considered that given the content of the supplement, the fact that Napp had been able to influence it, and the format of the articles contained therein, the supplement promoted oxycodone. The front cover of the supplement, however, stated that it had been supported through an educational grant from Napp Pharmaceuticals. The Appeal Board considered that the supplement was thus disguised promotion for oxycodone and a breach of the Code was ruled. The oxycodone prescribing information was not included in the supplement and a breach of the Code was also ruled in that regard.

A consultant physician complained about a Therapeutic Advances supplement issued with the

journal Prescriber. The supplement was entitled 'Oxycodone for pain malignancy and postoperative pain' and in four sections discussed the pharmacology of oxycodone, approaches to analgesia in malignancy, the place of oxycodone in the management of postoperative pain and pain in malignancy. There was also a GP's perspective of the product. Four independent authors had contributed to the supplement. The front cover stated that the publication was 'A Prescriber supplement supported through an educational grant from Napp Pharmaceuticals'.

Napp Pharmaceuticals Limited marketed four formulations of oxycodone – Oxycontin tablets, Oxynorm capsules and Oxynorm liquid and concentrate.

COMPLAINT

The complainant stated that the supplement was supplied with the journal Prescriber. It was sent unsolicited and appeared to represent, in all but name, an advertisement for oxycodone, without any summary of product characteristics.

RESPONSE

Napp explained that Prescriber ran a number of different series of supplements, which focused upon matters of current interest to healthcare professionals. Ideas for these supplements were generated by Prescriber's editorial team which scanned the public press for new developments. When a topic had been identified the editorial team would itself look for both suitable authors and funding support. Prescriber commissioned and paid the authors itself. There was no contact between the authors and the sponsoring pharmaceutical company at any time. Finally, the supplements were peer reviewed for accuracy and balance.

Napp stated that the content of the supplement at issue, which appeared in the 5 March issue of Prescriber, was initiated in the same way. Prescriber's editorial team approached Napp's public relations agency to see if the company would be interested in providing an educational grant for a supplement on oxycodone. The agency in turn approached Napp and it agreed to provide such a grant. Napp, however, had no involvement with the selection or commissioning of the authors, no contact with the authors regarding the content of their articles and there was no payment by Napp to the authors. Finally, the articles were peer reviewed by leading specialists in the field of pain relief before publication, again without any input from Napp. Napp, as sponsor, did see a copy of the supplement before publication but editorial control remained entirely with Prescriber.

Napp provided a letter from Prescriber confirming the above.

Napp explained that both production and circulation of the supplement were arranged by Prescriber's publishers. Napp's only involvement had been in the circulation of copies of the supplement to doctors, but only on their request.

With regard to Clause 4.1 of the Code, Napp did not consider that the articles contained within the supplement were promotional. There was no mention of its products. As was explained in the letter from Prescriber, it was common practice for pharmaceutical companies to provide grants in support of such supplements and it was also commonplace for such articles not to contain prescribing information. Napp provided copies of a number of different Prescriber supplements.

Turning to the provisions of Clause 9.1, Napp stated that the articles contained within the supplement were written by health professionals experienced in the field of pain relief for the benefit of other health professionals interested in the area. Given this, and the fact that the supplement was peer reviewed, Napp did not see how the supplement could have failed to take account of the professional standing of the audience.

With regard to Clause 10.1 Napp stated that its involvement in sponsoring this supplement was not disguised. It was clearly stated on the front cover. Indeed, it was this notice that was quoted by the complainant and which triggered the complaint.

In response to a request for further information Napp confirmed that the supplement was circulated by the publishers as a loose insert in the Prescriber journal.

Napp stated that its representatives did not initiate discussions with doctors regarding the Prescriber supplement. Each representative was issued with 50 copies of the supplement for use only when the doctor asked for peer reviewed papers relating to the relevant therapy area. The representatives certainly did not use the supplement as a promotional item.

Napp stated that the enquiries it received from doctors were general requests for information. The company did not know whether any of the doctors in question had already seen the supplement but presumed that only those who had read the supplement would be interested in receiving a copy. No specific briefing material was prepared in connection with the distribution of the copies of the supplement to the representatives; they were merely distributed as clinical support items for use in the manner described above.

PANEL RULING

The Panel first had to decide whether the journal supplement was subject to the Code. The supplement had been sponsored by a company with a commercial interest in the medicine featured and was thus potentially subject to the Code. In relation to the published material, Clause 9.9 required material relating to medicines to so declare if it had been sponsored by a pharmaceutical company and this applied even if the material was non-promotional. The Panel noted that it was clearly stated on the front cover of the supplement that it had been supported through an educational grant from Napp Pharmaceuticals.

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 responsible under the Code for its content, 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 a promotional purpose. The Panel noted that Napp's only involvement in the production of the supplement had been to provide the financial sponsorship; the company had not chosen the authors and had had no editorial control. The complainant had received the supplement with the copy of Prescriber and not from the company or its representatives. In these circumstances the supplement did not have to include the prescribing information. The Panel therefore ruled no breach of Clause 4.1 of the Code.

The Panel noted the clear declaration of sponsorship on the front and back of the item as required by Clause 9.9 and noted that the complainant had obtained the supplement via the journal. The Panel considered that the production of the journal and its distribution by Prescriber did not amount to disguised promotion contrary to Clause 10.1 of the Code, nor did it fail to maintain high standards as required by Clause 9.1. No breach of the Code was ruled in that regard.

The Panel noted that the supplement had, however, been made available by Napp's representatives. The Panel noted Napp's submission regarding the use of the supplement by its representatives. The Panel noted that if a request for the supplement was solicited or if it was otherwise used for a promotional purpose the prescribing information would be required and the content of the supplement would have to comply with the Code.

APPEAL BY THE COMPLAINANT

The complainant stated that his major concern was the ellipsis used to express the relationship between the company, the authors, and the editorial control. The complainant noted that Napp had stated that it 'had no contact with the authors regarding the content of their articles …' and 'as sponsor, did see a copy of the supplement before publication but editorial control remained entirely with Prescriber.' The complainant noted that the Panel found 'no input by the company'.

The complainant stated that it would be helpful, therefore, to have a clear and unequivocal answer from Napp on the following points:

> Did Napp make comments on the original draft manuscripts?
>
> Were those comments passed on to the authors by Prescriber?
>
> Did the authors make changes as a result?

It would also be helpful to know, as Napp stated that it made no payment to the authors, whether the authors had in fact received any honoraria or research grants from the company unrelated to the supplement, which would have represented a conflict of interest.

Until these questions were answered, the complainant stated that he would not be satisfied that the Panel was correct in determining that Napp merely provided the money and had no editorial control.

RESPONSE FROM NAPP

Napp stated that all original draft manuscripts were sent by the authors to Prescriber's editorial team who then passed them on to the independent peer reviewer. Following peer review, the articles were sent back to Prescriber for further editorial review and formatting. They were then forwarded to Napp.

Napp stated that it offered a number of comments to Prescriber on factual accuracy and the licensed indication. These were only suggestions and a number of them were disregarded. None of the suggestions were of a promotional nature. The company was informed by Prescriber that the authors did approve a final edited version that included comments from the Prescriber editorial department, the peer reviewer and those suggestions from Napp that the Prescriber editorial team had accepted. At all times, editorial control remained with Prescriber.

Napp reiterated that it was not involved in the recruitment of the authors and made no payments to the authors for the articles.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that Napp's response to the appeal made it clear that the company was economical with the truth insofar as it was able to comment on the articles and suggest changes to them; to that extent, the editorial process was within the company's influence, and since it was paying for the supplement, and publishers depended substantially on such supplements for income, the publisher was not editorially independent.

A similar economy, or obfuscation, was evident from the company's reply, when it stated that it 'made no payment to the authors for the articles'. The complainant noted that the question he posed was whether the authors had in fact received payment or support for any activities from Napp, since that would indicate a potential conflict of interest.

The complainant stated that in support of his view that the supplement was unreasonably positive in its assessment of oxycodone, he noted that the French journal of prescribing advice, Prescriber, stated that the product had, in its (unbiased) view, no benefit over existing oral opioids.

APPEAL BOARD RULING

The Appeal Board noted that Napp's involvement with the production of the supplement had become clearer upon appeal by the complainant. Napp had made comments on the draft manuscripts some of which had been accepted. The company had thus had some input into the articles.

The Appeal Board noted that the supplement discussed the use of one medicine, oxycodone, in the management of pain of malignancy and postoperative pain. Each article contained a shaded box

highlighting 'Key points' some of which, in the Appeal Board's view, could be considered to be claims for oxycodone. The Appeal Board considered that given the content of the supplement, the fact that Napp had been able to influence it, and the format of the articles contained therein, the supplement promoted oxycodone. The front cover of the supplement, however, stated that it had been supported through an educational grant from Napp Pharmaceuticals. The Appeal Board considered that the supplement was thus disguised promotion for oxycodone and a breach of Clause 10.1 was ruled. The oxycodone prescribing information was not included in the supplement and a breach of Clause 4.1 was ruled. The appeal was successful.

Complaint received **16 June 2000**

Case completed **21 July 2000**

CASE AUTH/988/3/00

GENERAL PRACTITIONER v NOVARTIS

Lescol detail aid

A general practitioner complained about a detail aid for Lescol (fluvastatin) issued by Novartis which was entitled 'Are you putting the squeeze on cholesterol?'

A bar chart on page 2 showed the mean percentage decrease in LDL-cholesterol from baseline after six months' therapy with Lescol (–27.9%), simvastatin (–24.4%) and pravastatin (–19%). It was alleged that the page was misleading with regard to the evidence comparing Lescol with the current market leaders, simvastatin and pravastatin. These were the only ones with long-term, large scale studies to confirm their effect on cardiovascular outcomes. The comparison shown was misleading as it did not compare equivalent doses of Lescol and simvastatin. The cited study (Spearman *et al* 1997) used a 5mg dose of simvastatin which was not licensed in the UK.

The Panel noted that the page compared the reduction in LDL-cholesterol. There was no mention of cardiovascular outcomes. The Spearman study measured the relative cost effectiveness of statins (fluvastatin, lovastatin, pravastatin and simvastatin) in a real world setting. The Panel noted that the dosage range used for simvastatin was 5-40mg and that 5mg was not a licensed dose in the UK. The Panel noted the submission from Novartis that only 7% of patients in the simvastatin treatment group were prescribed 5mg per day. The Panel considered that the effect of the 5mg dose of simvastatin had been included in the calculation of percentage decrease in LDL-cholesterol. The study was not comparing like with like. The page in the detail aid did not reflect the balance of the evidence regarding the efficacy of simvastatin and pravastatin. A breach of the Code was ruled.

Pages 4 and 5 of the detail aid formed a double page spread headed 'Putting the squeeze on coronary atherosclerosis'. The claim 'Significant reduction (–71%) in coronary events with Lescol compared with placebo' appeared as a heading to a graph which showed ten coronary events with placebo compared with three for Lescol. The complainant considered this very dubious as Lescol did not yet have a licence to reduce coronary events and the quoted reference was an in-press article. The complainant noted that a footnote on the page, in small print, stated that Lescol was not currently licensed to reduce the risk of coronary events.

The Panel noted that Lescol was not licensed to reduce coronary events. This might be a feature of treatment but was not a licensed indication as such. The Panel considered that the claim at issue and the graph promoted Lescol for reducing coronary events and ruled a breach of the Code. Upon appeal by Novartis, the Appeal Board noted that Lescol was licensed to slow the progression of coronary atherosclerosis in patients with primary hypercholesterolaemia and concomitant coronary heart disease who did not adequately respond to dietary control. Immediately below the bar chart small print explained that the term 'coronary events' meant coronary death, myocardial infarction, unstable angina or the need for bypass surgery, and that Lescol was not currently licensed to reduce the risk of coronary events. In the Appeal Board's view the claim would lead most readers to expect a 71% reduction in all coronary events for all patients treated with Lescol. The data, however, was more limited that this. It related to a relatively small study with regard to the determination of clinical outcome and the wide term 'coronary events' was qualified by small print. In addition Lescol was not licensed to reduce coronary events, a fact which was again explained in small print. The Appeal Board considered that the claim promoted Lescol for an unlicensed indication. The Panel's ruling of a breach of the Code was upheld.

A bar chart on page 6 compared the mean number of side effects for Lescol 20-40mg/day (0.27), simvastatin 5-40mg/day (0.78) and pravastatin 10-40mg/day (0.7). The data was referenced to Spearman. The complainant alleged that the data on side effects was misleading with regard to the number that occurred. The dosage that the patients were on certainly did not fit in with the evidence from other large scale studies eg 4S on the tolerability of the other statin. The Panel queried whether the data were a balanced reflection of all the evidence and was concerned whether it was reasonable to use data from a cost effectiveness study to support claims for differences in the incidence of side effects. The determination as to whether adverse drug effects were attributable to statin pharmacotherapy was based on chart reviews

and/or interviews with treating physicians. All determinations were based on reported side effects in the package inserts. Whilst the y axis referred to the mean number of side effects the heading referred to a low incidence of side effects. There was a difference between the actual incidence of side effects and the level of reported side effects. The Panel considered that the basis of the side effect data had not been sufficiently explained in the detail aid. The Panel ruled that the material was misleading in breach of the Code.

Page 7 of the detail aid featured a bar chart which depicted the number of patients with elevated cholesterol that could be treated per year for coronary atherosclerosis with various doses of Lescol, simvastatin and pravastatin assuming a budget of £20,000. The complainant considered that the page was irrelevant in terms of demonstrating how many patients with elevated cholesterol could be treated per year because, although Lescol being cheaper would allow more patients to be treated, it did not necessarily mean that it would prevent any coronary events or reduce mortality. It was alleged that the page was misleading. The Panel considered that the page clearly stated that the cost comparison related to patients with coronary atherosclerosis. There was no mention of prevention of coronary events or reduction of mortality. The Panel noted that on page 5 the use of Lescol in coronary atherosclerosis had been linked to a reduction in coronary events. While it would depend on how the representatives linked pages 5 and 7 the Panel did not accept that the page was misleading as alleged. No breach of the Code was ruled.

A general practitioner complained about an eight page Lescol (fluvastatin) detail aid (ref LES 99/06) issued by Novartis Pharmaceuticals UK Ltd. The detail aid was entitled 'Are you putting the squeeze on cholesterol?'

1 Comparisons with simvastatin and pravastatin

Page 2 featured a bar chart showing the mean percentage decrease in LDL-cholesterol from baseline after six months' therapy with Lescol (–27.9%), simvastatin (–24.4%) and pravastatin (–19%).

COMPLAINT

The complainant alleged that the page was misleading with regard to the evidence comparing Lescol with the current market leaders, simvastatin and pravastatin. To date these medicines were the only ones with long-term, large scale studies to confirm their effect on cardiovascular outcomes. The complainant stated that the comparison shown was misleading as it did not compare equivalent doses of Lescol and simvastatin. The cited study (Spearman *et al* 1997) used a 5mg dose of simvastatin which was not licensed in the UK.

RESPONSE

Novartis noted that the complainant appeared to suggest that it was not acceptable for the company to present data comparing the relative efficacy of Lescol to that of simvastatin and pravastatin in the reduction of LDL-cholesterol. This argument seemed to be based on the lack of a long-term morbidity and mortality study for Lescol. This argument was however not relevant when comparing the relative efficacies of the three medicines in their approved indication of hypercholesterolaemia which was the clear purpose of the page at issue.

Novartis stated that the supporting data for the comparison came from Spearman *et al* which studied the use of fluvastatin, simvastatin and pravastatin therapy in a real life primary care population of 299 patients. In this study a range of therapeutic doses was employed for each medicine reflecting their use in the real world. At the start of the trial, patients were given an initial dose of each medicine, as considered appropriate by the prescribing physician. As a result 5 patients (7%) in the simvastatin treated group were prescribed 5mg per day. The practitioners were then allowed to titrate the starting dose upwards if they believed it appropriate in each patient. In the simvastatin group only 12% of patients had their initial starting dose titrated upwards, suggesting that many patients were considered adequately controlled at their starting dose.

The majority of patients in the study received a dose of simvastatin of between 10 and 40mg (93%). Novartis stated that its knowledge of the UK market would suggest that this distribution of dose was indeed representative of the prescribing pattern currently employed. Therefore, whilst the company accepted that a small number of patients received an unlicensed UK dosage of simvastatin in this study (5 out of 69), this did not invalidate the overall conclusion regarding the relative efficacies of the medicines. Novartis added that in this study each of the medicines was considered effective and it had not been the company's intention to detract from this in the data presented.

PANEL RULING

The Panel noted that the page compared the reduction in LDL-cholesterol. There was no mention of cardiovascular outcomes.

The Panel examined the Spearman study which measured the relative cost effectiveness of statins (fluvastatin, lovastatin, pravastatin and simvastatin) in a real world setting. The study used a prospective, randomised, balanced cohort design examining patients who had been prescribed initial therapy with a statin as monotherapy. The study was undertaken by a managed care organisation in Texas. The report stated that as with most studies the study included confounding variables and results that appeared to be outside expected values. The overall effectiveness of fluvastatin was found to be comparable to results reported elsewhere. The study referred to the clinical results for lovastatin, pravastatin and simvastatin being below those values reported in controlled clinical trials. The authors noted that significant interstudy variability in the effectiveness of statins had been noted in many studies.

The report also referred to a pronounced trend by speciality care physicians to use lovastatin, pravastatin and simvastatin whereas primary care physicians

more commonly used fluvastatin. The study was not balanced for the speciality of the treating physician. For specialists treating complex cardiovascular cases lowering high blood cholesterol might be secondary to treating other more urgent patient conditions. The report stated that this important factor, which eluded quantitation, might account for the present results of decreased expected effectiveness of lovastatin, pravastatin and simvastatin.

The Panel noted that the dosage range used for simvastatin was 5-40mg and that 5mg was not a licensed dose in the UK. The Panel noted the submission from Novartis that only 7% of patients in the simvastatin treatment group were prescribed 5mg per day. The Panel considered that the effect of the 5mg dose of simvastatin had been included in the calculation of percentage decrease in LDL-cholesterol. The study was not comparing like with like. The Panel did not know whether the inclusion of the 5mg data would invalidate the overall conclusion.

The Panel considered that the page in the detail aid did not reflect the balance of the evidence regarding the efficacy of simvastatin and pravastatin. A breach of Clause 7.2 of the Code was ruled.

2 Claim 'Significant reduction (–71%) in coronary events with Lescol compared with placebo'

Pages 4 and 5 of the detail aid formed a double page spread headed 'Putting the squeeze on coronary atherosclerosis'. The claim at issue appeared as a heading to a graph on page 5 which showed 10 coronary events with placebo compared to 3 with Lescol. The difference was statistically significant ($p<0.05$).

COMPLAINT

The complainant pointed out that the findings of the LiSA [Lescol in Severe Atherosclerosis] study were depicted showing a 71% reduction in coronary events with Lescol compared with placebo. The complainant considered this very dubious as Lescol did not have a licence yet to reduce coronary events and the quoted reference was an in-press article. The complainant noted that a footnote on the page, in small print, stated that Lescol was not currently licensed to reduce the risk of coronary events.

RESPONSE

Novartis noted that the complainant would appear to cast doubt on the validity of the supporting evidence for the information presented because the study was cited as being in press. In addition the complainant suggested that the product had been promoted outside its licence.

Novartis stated that at the time of production of the detail aid the results of the LiSA study had only been accepted for publication. However, once the study had been published in a reputable journal (Atherosclerosis, May 1999) the materials for Lescol were updated to reflect this.

In terms of the approved indications for Lescol, Novartis stated that the product was licensed to slow the progression of coronary atherosclerosis in patients with primary hypercholesterolaemia and concomitant coronary heart disease who did not adequately respond to dietary control.

Since the use of Lescol had been shown to slow the progression of atherosclerosis the company considered it was reasonable to assume that this would convey benefits to the patient in terms of the symptoms of cardiac disease. The LiSA study, which investigated the use of Lescol in the management of severe atherosclerosis, clearly demonstrated these benefits in terms of reduction in coronary events. Since Lescol was licensed to slow atherosclerosis progression, Novartis did not accept that it had promoted outside of the licence by presenting the benefits of such treatment in terms of coronary disease progression. The company had rather demonstrated the positive effects of the management of an underlying disease state in terms of the relief of the recognised symptoms of that disease state.

Novartis added that the information on the page was clearly presented under the heading of atherosclerosis, and was clearly associated with details of the licensed indications for the product. The company did not consider therefore that the page was in any way misleading to the prescriber in terms of the licensed indications for Lescol. Novartis noted that this was the first time that such doubt had been expressed in relation to the credibility or presentation of this data, despite its inclusion in the promotional materials for Lescol over the past year.

PANEL RULING

The Panel noted that Lescol was not licensed to reduce coronary events. This might be a feature of treatment with the product but was not a licensed indication as such. The Panel considered that the claim at issue and the graph in effect promoted Lescol for reducing coronary events and ruled a breach of Clause 3.2 of the Code. The Panel noted that it was not possible under the Code to qualify a claim by the use of a footnote.

APPEAL BY NOVARTIS

Novartis stated that the approved indications for Lescol included the slowing of progression of coronary atherosclerosis in patients with primary hypercholesterolaemia and concomitant coronary heart disease who did not adequately respond to dietary control.

Lescol intervention had been shown clinically to slow the progression of coronary atherosclerosis consistently with the licence and thus convey benefits to patients in terms of reduced atherosclerosis progression. It was hard to imagine how these benefits of slowing atherosclerosis progression could be conveyed without making some statement about the effects of the product on the coronary events associated with atherosclerosis progression.

In conclusion Novartis stated that it could not accept that it was possible for a product to be licensed to treat a pathology, but not licensed to treat a well recognised symptom of that pathology. The company noted that

past case reports supported this position. A distinct similarity had been noted between the case in question and Case AUTH/819/1/99 in which Merck Sharp & Dohme Limited was found to be innocent of promoting outside of its licence for simvastatin when demonstrating a reduced incidence of angina in patients receiving therapy. Again the product was not licensed specifically for the treatment of angina, but did have a licence for slowing the progression of coronary atherosclerosis. Similarly Merck Sharp & Dohme had argued that angina was one of the clinical manifestations of the underlying disease process for which its product was licensed. This was supported both by the Panel and on appeal; the Appeal Board had considered that general practitioners would be familiar with the statins and their use and that they were licensed to treat the underlying pathology and not the presenting symptom.

Novartis stated that in the light of what appeared to be conflicting judgements on two very closely related cases it considered it appropriate to refer the Panel's ruling to the Appeal Board for its opinion.

APPEAL BOARD RULING

The Appeal Board noted the comments made by Novartis about the previous case. The claims in that case referred to both the incidence and the risk of angina. Each case needed to be considered on its own merits. Context was an important factor.

The Appeal Board noted that Lescol was licensed to slow the progression of coronary atherosclerosis in patients with primary hypercholesterolaemia and concomitant coronary heart disease who did not adequately respond to dietary control. The claim in question stated 'Significant reduction (–71%) in coronary events with Lescol compared to placebo'. The claim reflected the findings of the LiSA study and appeared immediately above a bar chart which showed that in the placebo group (n=178) there were 10 coronary events compared with 3 in the Lescol group (n=187) ($p<0.05$). Immediately below the bar chart was some small print which explained that the term 'coronary events' meant coronary death, myocardial infarction, unstable angina or the need for bypass surgery. The small print also explained that Lescol was not currently licensed to reduce the risk of coronary events.

In the Appeal Board's view the claim would lead most readers to expect a 71% reduction in all coronary events for all patients treated with Lescol. The data, however, was more limited than this; it related to a relatively small study with regard to the determination of clinical outcome and the wide term 'coronary events' was qualified by small print. In addition Lescol was not licensed to reduce coronary events, a fact which was again explained in small print. The Appeal Board considered that the claim promoted Lescol for an unlicensed indication. The Panel's ruling of a breach of Clause 3.2 was upheld. The appeal was unsuccessful.

3 Side effects

A bar chart on page 6 compared the mean number of side effects for Lescol 20-40mg/day (0.27), simvastatin 5-40mg/day (0.78) and pravastatin 10-40mg/day (0.7). The data was referenced to Spearman *et al* (1997).

COMPLAINT

The complainant alleged that the data on side effects was misleading with regard to the number that occurred. The dosage that the patients were on certainly did not fit in with the evidence from other large scale studies eg 4S on the tolerability of the other statin.

RESPONSE

Novartis stated that, as already noted, the Spearman study reflected the use of statin therapy in a real life setting, employing a number of different doses for each medicine. The data from the Spearman study had been selected simply because it presented data for all three statins in a realistic range of doses as stated under the graph. Novartis refuted the suggestion that the doses used were unrepresentative or that the inclusion of 5 patients receiving a dose of 5mg of simvastatin could affect the overall tolerability of simvastatin, other than positively. The tolerability profile of the statins was acknowledged by prescribers to be very good as was reflected in the small mean number of side effects overall for each statin in the graph.

PANEL RULING

The Panel noted its comments made in point 1 above about the Spearman *et al* study. The study stated that patients taking fluvastatin averaged fewer blood tests to resolve questions of efficacy and/or safety. The differences in laboratory testing might reflect differences in product labelling as at the time of the study the labelling for fluvastatin called for fewer follow-up laboratory tests for liver function monitoring than labelling for the other three statins.

The Panel considered that the side effect data were qualified by statements in the study. The Panel queried whether the data were a balanced reflection of all the evidence. The Panel was also concerned whether it was reasonable to use data from a cost effectiveness study to support claims for differences in the incidence of side effects. The determination as to whether adverse drug effects were attributable to statin pharmacotherapy was based on chart reviews and/or interviews with treating physicians. All determinations were based on reported side effects in the package insert for each product's labelling. Whilst the y axis referred to the mean number of side effects the heading referred to a low incidence of side effects. There was a difference between the actual incidence of side effects and the level of reported side effects. The Panel considered that the basis of the side effect data had not been sufficiently explained in the detail aid. The Panel ruled that the material was misleading in breach of Clause 7.2 of the Code.

4 Cost comparison

Page 7 of the detail aid featured a bar chart which depicted the number of patients with elevated cholesterol that could be treated per year for coronary

atherosclerosis with various doses of Lescol, simvastatin and pravastatin assuming a budget of £20,000. The numbers of patients that could be treated were Lescol 20mg (103), 40mg (96) and 80mg (51); simvastatin 10mg (84), 20mg (49) and 40mg (33); pravastatin 10mg (95), 20mg (49) and 40mg (33). Although cerivastatin and atorvastatin were also featured on the x axis of the chart a figure of zero was given for each one as neither was licensed to treat coronary atherosclerosis.

COMPLAINT

The complainant considered that the page was irrelevant in terms of demonstrating how many patients with elevated cholesterol could be treated per year because, although Lescol being cheaper would allow more patients to be treated, it did not necessarily mean that it would prevent any coronary events or reduce mortality. The complainant alleged that the page was misleading.

RESPONSE

Novartis stated that it was quite clear from the heading of the bar chart that the cost comparison was based upon the number of patients with elevated cholesterol who could be treated per year for coronary atherosclerosis. No mention was made of reduced mortality and since all three statins presented were licensed for the indication shown, and the costs presented were accurate at the time of printing, the company could not accept that it was unreasonable under the Code to present such a cost comparison.

PANEL RULING

The Panel considered that the page clearly stated that the cost comparison related to patients with coronary atherosclerosis. There was no mention of prevention of coronary events or reduction of mortality. The Panel noted that on page 5 the use of Lescol in coronary atherosclerosis had been linked to a reduction in coronary events. While it would depend on how the representatives linked pages 5 and 7 the Panel did not accept that the page was misleading as alleged. No breach of Clause 7.2 of the Code was ruled.

Complaint received **20 March 2000**

Case completed **13 July 2000**

CASE AUTH/993/3/00

PHARMACIST v BAYER

Promotion of Lipobay

A pharmacist adviser complained about the promotion of Lipobay 400mcg (cerivastatin) by Bayer. The items at issue were a leavepiece for use in primary healthcare, which compared the costs of statins, and a hospital detail aid.

The complainant alleged that the items made inappropriate comparisons and created the impression that the starting dose for Lipobay was 400mcg. The efficacy figure cited in both items did not reflect the wider data available. Other data showed that prescribers could not reasonably expect a 38% reduction in LDL-C with Lipobay 400mcg. The recently published Lipobay dose comparison placebo controlled study by Stein *et al* (1999), cited by Bayer in other materials, reported a statistically significant mean percentage change in plasma LDL-C from baseline (4.90mmol/l) of 36.2% in the Lipobay 400mcg treatment group (n=791). The Ose study cited in the leavepiece involved a significantly smaller patient population with a lower baseline LDL-C level of 4.67mmol/l treated with Lipobay 400mcg (per protocol analysis n=302 and intention to treat (ITT) analysis n=330). Other published data for Lipobay 400mcg indicated a mean decrease in LDL-C of 35.8mmol/l ($p<0.0001$, n=138). Further, in the detail aid the 44% efficacy cited for Lipobay 400mcg was grossly misleading as it only applied to a small number of women.

The Panel considered that it would have been helpful if the dosage information in the leavepiece had stated, at the outset, that 400mcg was not a starting dose. The leavepiece did not mention anything about the starting dose of 100mcg except for statements in the prescribing information. The Panel considered, however, that as the leavepiece listed all the doses of cerivastatin readers would be aware that 400mcg was the maximum dose and that smaller doses, starting at 100mcg, were available. The Panel did not consider that the leavepiece gave the impression that the starting dose of Lipobay was 400mcg and no breach of the Code was ruled. The Panel noted that the detail aid focused on Lipobay 400mcg as being a new strength to lower LDL-cholesterol. The other doses were mentioned in a bar chart comparing the monthly cost of treatment. The 200mcg dose was also mentioned in relation to a comparison with pravastatin. The prescribing information referred to Lipobay 400mcg and similarly to the leavepiece stated that treatment should be started at 100mcg. The Panel considered that as the detail aid gave more information about the use and effects of Lipobay 400mcg it was misleading not to mention somewhere in the body of the detail aid that treatment needed to be started at 100mcg and titrated up. It was not sufficient in the circumstances to only have that information in the prescribing information. The Panel ruled a breach of the Code.

The Panel noted the study by Ose used to support the mean LDL-C lowering of 38%. A significant gender difference was evident with the 400mcg dose, LDL-C decreased by 44.4% ± 8.9% in women as compared with 37 ± 10.3% in men. A study by Stein showed a reduction of 38.2% in women as compared with 34.9% in men. The Panel noted that Bayer had stated that differences in efficacy were seen due to differences in study design and patient groups. The Panel did not consider that the use of Ose *et al* data was unreasonable *per se*. It was not inconsistent with the balance of the evidence. No breach of the Code was ruled. With regard to the figure of 44% for females, the Panel noted that this data had been considered in two previous cases, AUTH/970/1/00 and AUTH/972/1/00. In Case AUTH/970/1/00, the Panel had considered the claim at issue was misleading and ruled a breach of the Code. The ruling had also applied to Case AUTH/972/1/00. Turning to the present case, the Panel noted its previous comments regarding the gender response not being a primary nor secondary efficacy parameter. The data was based on an exploratory sub-group analysis in 102 women. The Panel considered that the detail aid was misleading in presenting the gender data in the context of a primary end point analysis. A breach of the Code was ruled.

A comparison of 400mcg of Lipobay with 10mg atorvastatin and 10mg simvastatin appeared in the leavepiece. The data for Lipobay 400mcg and atorvastatin 10mg were given in black and thus appeared emboldened amongst the other data which were in blue. The detail aid gave data with regard to the cholesterol lowering efficacy of Lipobay 400mcg. A page was headed 'Lipid lowering with the three most common statin prescriptions' and 'mean percentage changes from baseline at week 8'. Data for simvastatin 10mg/day, 20mg/day and atorvastatin 10mg/day with respect to total cholesterol, LDL-cholesterol and HDL-cholesterol were given in a table (referenced to Jones *et al* 1998). A separate table headed 'Lipid lowering in 4S' gave the data for simvastatin 20-40mg/day (referenced to the 4S study 1994). A page in the detail aid headed 'Monthly cost of treatment' included a bar chart showing the costs of 28 days treatment with various statins. Apart from Lipobay which had two columns, one for the cost of the 100mcg, 200mcg and 300mcg dose and one for the cost of the 400mcg dose, each statin (fluvastatin, pravastatin, simvastatin and atorvastatin) had one column depicting the cost of the various doses. The costs were all given in figures. The Lipobay 400mcg column was yellow and headed 'new', all the others were pale blue for the lowest dose and white for the highest dose. Another page of the detail aid referred to Lipobay 400mcg as a 'Simple to use once-daily dosage' and as 'Cost effective'.

The complainant alleged that the comparison in the leavepiece was inappropriate and misleading. There was no valid rationale explaining the practical benefits to a prescriber of this non-milligram equivalent comparison which compared the lowest starting dose of atorvastatin and the maximum licensed dosage of Lipobay. To provide a comparison on the basis of 'cost per percentage LDL-C reduction' without any further qualification was only fair if it compared like with like, either starting doses or maximum licensed doses. The same was true for the comparison drawn in the detail aid where efficacy data was presented for simvastatin and atorvastatin. The latter was misleading as it created the impression that the data represented the results of head-to-head comparisons with Lipobay 400mcg. The complainant believed that the style and manner in which this comparison was presented would mislead physicians to believe that lipid lowering therapy could be initiated at the 400mcg dose of Lipobay obviating the need to initiate treatment with Lipobay 100mcg, the licensed starting dosage. Further, the detail aid referred to Lipobay 400mcg as being 'cost effective'. This was meaningless without a clear definition. Clearly there were other measures of cost effectiveness over and above absolute medicine cost. It was also alleged that a claim for simplicity of dosing, when considered in the context of the item as a whole, was misleading as it did not address the issue of the titration schedule and again implied that 400mcg was a recommended starting dose.

The Panel did not consider that the comparison of cerivastatin 400mcg per day and atorvastatin 10mg per day in the leavepiece was misleading as alleged. The Panel accepted the submission that the comparison was based on efficacy. Data had been given for each dose. It would be inappropriate to compare on a mg for mg basis. As the leavepiece listed all the doses of cerivastatin and atorvastatin readers would be aware that 400mcg was the highest recommended dose of cerivastatin and 10mg was the lowest recommended dose of atorvastatin. No breach of the Code was ruled in this regard. With regard to the detail aid, the Panel did not accept that the impression was given that the data came from a head to head study with Lipobay. The heading clearly referred to the three most common statin prescriptions. No breach of the Code was ruled in that regard. The Panel noted that the layout of the two pages was such that the data would be compared. The Panel noted that there were differences between the studies and considered that the juxtapositioning of the data was unfair. The Panel ruled a breach of the Code in this regard. This ruling also applied to the leavepiece.

Upon appeal by Bayer, the Appeal Board noted that there were differences in the studies involved in terms of duration of therapy (24 weeks and 8 weeks respectively). However, given that the therapeutic response to statins was seen within 4-6 weeks of therapy, and the response was maintained during continuation of therapy, the difference in duration of therapy between the two studies would make no clinical difference with regard to lipid lowering effect. The detail aid referred to the relevant time periods. It was primarily aimed at hospital doctors which was a specialist audience and one that was interested in targets with regard to percentage lowering of cholesterol. The pages in question showed what doses of cerivastatin, simvastatin, and atorvastatin should be used to achieve a target reduction of about 25% in total cholesterol. Readers would relate the doses shown to a target reduction

in cholesterol. The Appeal Board did not consider that presentation of the data was unfair or misleading. No breach of the Code was ruled. This ruling also applied to the leavepiece.

The Panel did not consider that it was unfair to use a different colour for the column showing the cost of the 400mcg dose of Lipobay. All the information was presented for the other doses of Lipobay. The Panel ruled no breach of the Code. The Panel did not accept Bayer's submission with regard to the claim that Lipobay was cost effective. The supplementary information to Clause 7.2 stated that care must be taken that any claim involving the economic evaluation of medicine was borne out by the data and did not exaggerate its significance. In the Panel's view claims for cost effectiveness had to be related to the cost of treatment in general, not just the cost of the medicine. No data had been provided in relation to the economic evaluation of the effectiveness of Lipobay 400mcg. The term 'cost effective' was interpreted as being more than that a product was less expensive than competitor products and that it worked. The Panel ruled that the use of the term 'cost effective' in the detail aid was misleading in breach of the Code.

With regard to the claim 'Simple to use once-daily' the Panel noted that whatever the dose of Lipobay, 100mcg, 200mcg, 300mcg or 400mcg, it was a once-daily dosage even during the titration period. The Panel did not consider that the claim was misleading even when it was considered in the context of the whole item. The Panel did not consider that the titration schedule was far from simple as alleged. No breach of the Code was ruled.

The complainant stated that the prescribing information in both items outlined, albeit in very small and difficult to read font, the titration schedules. However, the manner in which the prescribing information was presented created the impression that the 400mcg dosage was a stand alone dosage and that prescribers might not be required to follow the recommended titration schedule for Lipobay. This was further reinforced by the actual prescribing information provided. The latter was specific to the 400mcg dosage. Bayer had a separate SPC for the 100mcg, 200mcg and 300mcg dosages. This fact, and a clarification that the prescribing information was identical for all licensed doses of Lipobay, should be stated in the item in order not to create the false impression that the prescribing information relevant to the 400mcg dose was somehow different to that of the other doses of Lipobay. The Panel did not consider that the prescribing information was difficult to read in either the leavepiece or the detail aid and ruled no breach of the Code. Both items included only the prescribing information for the 400mcg dose. In the Panel's view both items promoted all four doses of Lipobay and the prescribing information for all doses should have been provided. The indications etc were the same for all the doses but other elements of the prescribing information were not the same. The Panel ruled a breach of the Code in this regard.

A page of the detail aid headed 'cerivastatin 400mcg side-effect profile' stated that '… cerivastatin has an exceptionally good safety profile …' and also that 'In contrast to existing statins, there was no evidence of any dose related increase in adverse effects with cerivastatin'. Both statements were quotations. The detail aid also referred to the risk evaluation and stroke prevention in the elderly – cerivastatin trial – the RESPECT study. The detail aid referred to two other studies and stated that research was continuing on the pleiotropic effects of cerivastatin. The complainant queried why the cerivastatin safety profile was exceptional. All statins offered an adverse effect profile that was comparable to placebo. In the complainant's opinion a 'new' dosage offered no unique advantages in terms of 'safety' over other established products in this class. The safety of Lipobay 400mcg could only be assured after a significant period of post-marketing surveillance and in this context the claim was clearly an exaggeration. Further, to suggest that 'In contrast to existing statins there was no evidence of any dose related increase in adverse effects with cerivastatin' was false and misleading and disparaging of the other statins. The latter claim was also referenced to the Stein *et al* (1998) study. This was not a comparative study including all existing statins. Further, the study was not powered to investigate safety as the primary efficacy parameter. To suggest otherwise was an exaggeration. This inappropriate and misleading use of study data by Bayer in promotional materials was further exemplified by the reference on page 13 of the detail aid to the RESPECT study. The impression that this page created was that the study had completed and Lipobay 400mcg was licensed for the endpoints investigated. This impression was further strengthened by the fact that with regard to the other studies also described, there was a clear statement that these were ongoing with the year in which results were expected clearly stated. The same could be said of the page referring to the pleiotropic effects of cerivastatin. There was no clarification that these were not effects for which Lipobay had a licence. In fact, a number of the other statins had, arguably, a superior pleiotropic effects profile compared to Lipobay. However, none of these were promoted on the basis of these effects. Why should Lipobay be different? The complainant suggested that there were not any robust clinically relevant human data available.

The Panel noted that Stein was a global pooled analysis of the efficacy, safety and tolerability of cerivastatin. The data was from Phase II and III clinical trials. The Panel noted that the study was from a pooled analysis and was not powered to investigate safety as the primary efficacy parameter. It was not a comparative study as such. The Panel considered that the quotation implied that cerivastatin had an excellent safety profile. The Panel considered that it was misleading to use the quotation given the data that it was based on and a breach of the Code was ruled.

The Panel considered that the quotation 'In contrast to existing statins there was no evidence or any dose related increase in adverse events with cerivastatin' was an accurate quotation from Stein (1998) data. The Panel noted that the Ose *et al* study stated that

the incidence of adverse events considered to have a possible or probable relationship to cerivastatin therapy were comparable in the 400mcg dose group and the 200mcg dose group. The Bayer data on file – Third Addendum to Clinical Expert Report – stated that certain adverse events appeared at peak incidence in the 400mcg dosage group and that even this peak incidence was not a cause of clinical concern; no events had been seen which might be unexpected for statins as a class and all had previously been recorded for cerivastatin during clinical development of the lower doses. The only event that might be considered dose related was asthenia. The Panel considered that it was misleading to state that there was no evidence of any dose related increase in adverse events based on the Stein (1998) data. Other data was not so unequivocal. The Panel considered that the quotation was not a balanced reflection of all the data. A breach of the Code was ruled.

With regard to the section on ongoing trials, the Panel was concerned that this section might imply that Lipobay was licensed for the endpoints used in the trials and the doses used. With regard to the RESPECT study the Panel noted that the detail aid indicated by use of an asterisk that one of the doses, 800mcg, was not licensed. The Panel accepted that health professionals would be interested in ongoing research. It was not appropriate for details of ongoing research to be given in promotional material if the research related to unlicensed indications and doses. The Panel considered that it amounted in effect to promotion of unlicensed indications and/or doses. The tabs on the pages, although labelled 'Ongoing Trials', did not negate this impression. A breach of the Code was ruled. This ruling was appealed by Bayer.

The Appeal Board noted that the detail aid in question was aimed primarily at hospital doctors, a group that was keen to receive evidence based data and to know what other data was being looked for in on-going trials. The Appeal Board noted that the detail aid presented the key points about the design and objectives of four ongoing trials. The details for three of the trials clearly included the year in which the results were expected. With regard to a fourth trial it was stated that the minimum planned treatment time was four years per patient or until 518 strokes had been observed. No results for any of the trials were given and in the Appeal Board's view no claims for Lipobay were made. The key areas involved in published and ongoing trials were listed. The Appeal Board was concerned about the layout of the pages in question. Noting that the intended audience was specialists, the Appeal Board decided that on balance the detail aid did not promote Lipobay outside the terms of its licence. The Appeal Board ruled no breach of the Code.

The complainant referred to Page 9 of the detail aid which depicted that Lipobay was metabolised by the CYP3A4 and 2C8 isoenzymes. However, on the preceding page entitled 'Drug interactions profile' there appeared to be an unequivocal statement that Lipobay had no interactions with digoxin and warfarin. Metabolism of the latter products was associated with the CYP3A4 isoenzyme and therefore assumed that these medicines bound to the CYP3A4 isoenzyme. The Lipobay SPC might refer to the wording 'no interactions' but this did not detract from the basic fact that if two medicines bound, reversibly or irreversibly and to a varying or similar extent, to a common receptor, then there always remained the potential for an interaction. This interaction might or might not be clinically significant but nevertheless the potential for interactions was always there. Thus the categorical nature of the claim for Lipobay and its depiction with ticks and crosses was an exaggeration of the facts. A qualification was required in order to avoid confusion. Page 8 also referred to cyclosporin blood trough levels. There was a clear and misleading suggestion that Lipobay did not interact with cyclosporin and that there was robust evidence to support this. This was simply not true. Further, in this regard the comparison was made with atorvastatin. Would it not, however, also be appropriate to include simvastatin in order to deliver a balanced comparison, particularly as both statins were compared in the section immediately above? The misleading impression created was that both Lipobay and simvastatin did not interact with cyclosporin.

The Panel noted that the Lipobay 400mcg SPC stated that cerivastatin was metabolised via a dual metabolic pathway utilising at least two cytochrome P450 isoenzymes, CYP2C8 and CYP3A4. A compensatory effect might be observed when one pathway was inhibited. The SPC also stated that based on *in vitro* enzyme affinity investigations there was no evidence of any cytochrome P450 inhibitory potential of cerivastatin including the major drug metabolizing enzyme CYP3A4. As expected from these findings no interaction with other co-medicated drugs which were substrates of CYP3A4 or other CYP enzymes were observed *in-vivo*. The SPC stated that co-administration of a single dose of warfarin to healthy subjects who had received Lipobay 300mcg for seven days did not result in any changes in prothrombin time or clotting factor VII activity when compared with placebo. The pharmacokinetics of both warfarin isomers were unaffected by concomitant administration of 300mcg Lipobay. The SPC also stated that plasma digoxin levels and digoxin clearance at steady state were not affected by concomitant administration of Lipobay 200mcg. The Panel noted the submission from Bayer that, accepting that there might be a theoretical possibility of an interaction between Lipobay and warfarin, this had not been shown to be so in a clinical trial (Schall *et al* (1995) on 21 male volunteers). The Panel considered that given the data in the SPC it was not unacceptable to state that there were no interactions between warfarin and cerivastatin and digoxin and cerivastatin. No breach of the Code was ruled in this regard. The cyclosporin data was referenced to an abstract by Renders *et al* (1998) which concluded that cerivastatin seemed not to influence cyclosporin A blood trough levels whereas atorvastatin did increase levels in a considerable portion of the

patients. Ten patients were treated with cerivastatin 200mcg, ten patients were treated with atorvastatin 10mg and ten patients were assigned to the control group. The reason for the side-effect was unknown but might be due to drug interaction via the cytochrome P450 enzyme system. The Panel considered that the detail aid was not a fair reflection of the results in the small study of 30 patients. The abstract used the description 'seemed not to influence' where as the detail aid stated 'does not influence'. The Panel ruled a breach of the Code.

A pharmacist adviser complained about the promotion of Lipobay 400mcg (cerivastatin) by Bayer plc, Pharmaceutical Division. The material at issue was a leavepiece for use in primary healthcare (OLIPO210) which compared the costs of statins and a hospital detail aid (OLIPO177).

Lipobay was indicated for the treatment of primary hypercholesterolaemia (types IIA and IIB) in patients who had not responded adequately to an appropriate diet. The product had originally been licensed with an initial dose of 100mcg per day which could be increased by increments of 100mcg at intervals of at least four weeks. The maximum recommended dose was 300mcg (summary of product characteristics (SPC) dated September 1999 from the Electronic Medicines Compendium). In December 1999 Lipobay 400mcg had been licensed. The indication was similar as was the initial dose. The Lipobay 400mcg SPC stated that the dose could be raised to a maximum of 400mcg once daily.

1 Efficacy statements

The leavepiece consisted of a chart on laminated card which was headed 'Cost of statins per percentage LDL-C reduction'. The chart gave details of the dose, cost/28 days (£), mean LDL-C lowering (%) and cost per percentage LDL-C reduction (pence/month) for cerivastatin at 100mcg, 200mcg, 300mcg and 400mcg, atorvastatin at 10mg, 20mg, 40mg and 80mg, fluvastatin at 20mg, 40mg and 80mg, pravastatin at 10mg, 20mg and 40mg and simvastatin at 10mg, 20mg and 40mg. The cost per 28 days came from MIMS January 2000. The mean LDL-C lowering for cerivastatin was referenced to data on file and a study by Ose *et al* (1999). The data for the other statins listed came from Jones *et al* (1998). The data for cerivastatin 400mcg and for atorvastatin 10mg were printed in black whereas the rest of the leavepiece was printed in blue.

The detail aid, page 3, included a bar chart beneath a heading 'New strength to lower LDL-cholesterol'. The bar chart showed the mean percentage change from baseline for a clinical trial involving 494 patients treated with cerivastatin for 24 weeks. The change for all patients was –38%, for males it was –37% and for females it was –44%. The bar chart was adapted from Ose *et al* (1999).

The detail aid, page 4, included a bar chart beneath a heading 'New strength to lower high cholesterol'. The bar chart showed the mean percentage change from baseline for total cholesterol (–26%), LDL-cholesterol (–38%) and HDL-cholesterol (+8%) for a clinical trial involving 494 patients treated with cerivastatin over 24 weeks. The bar chart was adapted from Ose *et al* (1999).

Page 5 compared simvastatin at 10mg/day with simvastatin at 20mg/day and atorvastatin at 10mg/day with respect to mean percentage changes from baseline at week 8 for total cholesterol, LDL-cholesterol and HDL-cholesterol. This was referenced to Jones *et al* (1998). The data for simvastatin 20-40mg from the Scandinavian Simvastatin Survival Study (4S) was also given on page 5.

COMPLAINT

The complainant alleged that the items were misleading and unhelpful. The materials made inappropriate comparisons and created the impression that the starting dose for Lipobay was 400mcg. The complainant alleged that the efficacy figure cited in both items did not reflect the wider data available for Lipobay 400mcg. Other data available contradicted the LDL-C efficacy data cited. These showed that prescribers could not reasonably expect a 38% reduction in LDL-C with Lipobay 400mcg. The recently published Lipobay dose comparison, placebo controlled study by Stein *et al* (1999) cited by Bayer in other materials, reported a statistically significant mean percentage change in plasma LDL-C from baseline (4.90mmol/l) of 36.2% in the Lipobay 400mcg treatment group (n=791). The Ose study cited in the leavepiece involved a significantly smaller patient population with a lower baseline LDL-C level of 4.67mmol/l treated with Lipobay 400mcg (per protocol analysis n=302 and intention to treat (ITT) analysis n=330). Other published data for Lipobay 400mcg indicated a mean decrease in LDL-C of 35.8mmol/l ($p<0.0001$, n=138). Further, in the detail aid the 44% efficacy cited for Lipobay 400mcg was grossly misleading as it only applied to a small number of women. Clearly this was an exaggeration of the efficacy of Lipobay 400mcg.

RESPONSE

Bayer submitted that the basis of the whole complaint appeared to be that it was misleading healthcare professionals by creating the impression that the starting dosage of Lipobay was 400mcg, this being done by inappropriate comparisons with statins. Bayer disputed this as it was clear in all Lipobay prescribing information and SPCs for all doses that this was not so. These provided clear advice regarding initiation dosage and titration steps.

Bayer stated that the 400mcg dose of Lipobay was only launched in December 1999, and therefore a new separate SPC was produced and approved by the Medicines Control Agency. A new promotional campaign to aid awareness of the new dosage was therefore started at this time including the items at issue. In addition, further justification for this focus on Lipobay 400mcg was based on epidemiological data for cholesterol levels in the UK population. Data from the British Heart Foundation indicated that it was likely that a considerable proportion of patients, although starting on Lipobay 100mcg, might require

Lipobay 400mcg as the maintenance dose in the long-term to achieve nationally recommended targets for cholesterol levels. Bayer promotional materials had not been designed to confuse healthcare professionals as claimed by the complainant. A brief overview of the materials clearly supported this fact.

The detail aid reviewed some of the new data obtained from clinical trials with Lipobay 400mcg in addition to outlining the interaction profile of cerivastatin in general and an update regarding ongoing clinical trials. A bar chart (on page 10) provided information on the monthly cost of treatment with all doses of all statins including Lipobay 100-300mcg. Furthermore the results from a comparative trial with pravastatin were reported including the comparison of Lipobay 200mcg with pravastatin 20mg.

Similarly, the leavepiece compared the costs of statins per percentage LDL-C reduction for all doses of all statins including Lipobay 100-300mcg. The emboldened items highlighted the newly launched Lipobay 400mcg compared with atorvastatin 10mg which had comparable efficacy. It was therefore difficult to conceive how this item was unbalanced and created the impression that the starting dose for Lipobay was 400mcg.

The allegation that the efficacy figure cited for Lipobay 400mcg did not reflect the wider available data for this dosage was incorrect. It was true that other data available demonstrated slight differences in efficacy for Lipobay 400mcg, however, these differences in efficacy were seen with all the statins due to differences in study design and patient groups between studies. For example, the LDL-C lowering efficacy of atorvastatin 10mg varied between –27%, Alaupovic *et al* (1997) and –41%, Nawrocki *et al* (1995). The cited study by Stein (1999) demonstrated a statistically significant mean percentage change in LDL-C from baseline of 36.2%, however this reduction was noted after 8 weeks of therapy. On the other hand the Ose (1999) study while involving fewer patients had a much longer treatment duration of 24 weeks where LDL-C was reduced by 38.5% in the per-protocol population and 37.9% in the intention-to-treat population. Furthermore the clinical datapool for Lipobay 400mcg (n=843) obtained following 24 weeks of therapy was more likely to approximate to actual clinical practice. It was therefore entirely reasonable to expect that Lipobay 400mcg was capable of achieving LDL-C reductions of 38% in clinical practice. The relevance of the differences in baseline LDL-C between the Ose study and the Stein publication that the complainant highlighted were not substantiated. Furthermore, the reference to 'other published data' indicating a mean decrease in LDL-C of 35.8mmol/l was an error. Bayer could only presume it was a reference to a decrease of 35.8%.

The complainant also alleged that the 44% efficacy cited for Lipobay 400mcg in the detail aid was grossly misleading, but no clear explanation as to why this might be the case was presented. In this instance, the item presented the data from the Ose study and was clearly referenced as such. Efficacy data with regard to lowering LDL-C was provided for male, female and all patients that participated in the study. The item did not exaggerate the efficacy of Lipobay as alleged, rather it accurately reported the results of a clinical trial. This issue relating to a decrease of 44% in LDL-C in this study was currently being addressed in Cases AUTH/970/1/00 and AUTH/972/1/00 which were waiting for an appeal to be heard.

PANEL RULING

The Panel first considered the allegation that the impression was given that the starting dose of Lipobay was 400mcg. The leavepiece referred to all four doses of cerivastatin in the chart. The prescribing information for Lipobay 400mcg tablets was given on the reverse and began by describing the tablets as containing 381.7mcg cerivastatin in the form of 400mcg cerivastatin sodium. In the section headed Posology and Administration the initial information given for adults was 'Take once a day …'. The second piece of information given was 'Start at 100mcg …'. Patients could thus not be started on Lipobay 400mcg tablets. They would have to be prescribed Lipobay 100mcg and be titrated up as necessary. The Panel considered that it would have been helpful if the dosage information had stated, at the outset, that 400mcg was not a starting dose. The leavepiece did not mention anything about the starting dose except for the statements in the prescribing information. The Panel considered, however, that as the leavepiece listed all the doses of cerivastatin readers would be aware that 400mcg was the maximum dose and that smaller doses, starting at 100mcg, were available. The Panel did not consider that the leavepiece gave the impression that the starting dose of Lipobay was 400mcg. No breach of Clause 7.2 was ruled.

The Panel noted that the detail aid focused on Lipobay 400mcg as being a new strength to lower LDL-cholesterol. It included data about the effects of 400mcg Lipobay. The other doses were mentioned in a bar chart comparing the monthly cost of treatment (page 10). The 200mcg dose of cerivastatin was also mentioned on page 17 of the detail aid in relation to a comparison with pravastatin. The prescribing information referred to Lipobay 400mcg and similarly to the leavepiece stated that treatment should be started at 100mcg. The Panel considered that its comments regarding the prescribing information in the leavepiece applied also to the detail aid. The Panel considered as the detail aid gave more information about the use and effects of Lipobay 400mcg it was misleading not to mention somewhere in the body of the detail aid that treatment needed to be started at 100mcg and titrated up. It was not sufficient in the circumstances to only have that information in the prescribing information. The Panel ruled a breach of Clause 7.2 of the Code.

The Panel examined the Ose study used to support the figures given in the leavepiece for the mean LDL-C lowering as 38%. This figure was also used on pages 3 and 4 of the detail aid.

The Panel noted that Ose *et al* (1999) was a multi-centre randomised double-blind parallel-group study comparing the efficacy and safety of cerivastatin 400mcg/day and 200mcg/day in 494 patients over a 24 week period. The study was open to patients with

documented primary hypercholesterolaemia defined as mean LDL-cholesterol ≥4.12mmol/l or a mean plasma LDL-cholesterol of ≥3.35mmol/l and either a history of CHD or two or more of six stated cardiovascular risk factors. The primary efficacy parameter was the percentage change in LDL-C from baseline to endpoint in the per-protocol population. The study concluded that overall (in the per-protocol population) mean LDL-C reduced by 38.4% ±0.7 from baseline in patients receiving cerivastatin 400mcg (n=302) compared to 31.5% ± 0.9 (n=141) in those receiving a 200mcg daily dose. This difference was confirmed in the intention to treat population (LDL-C decreased by 37.9% in the 400mcg group (n=330) and by 30.3% in the 200mcg group). In addition to a responder analysis, exploratory sub-group analyses were performed to determine the possible effects of gender and age on LDL-cholesterol changes. A significant gender difference was evident in patients taking the 400mcg dose. In the per-protocol population LDL-C decreased by 44.4 ± 8.9% (n=102) in women taking cerivastatin 400mcg compared with a decrease of 37 ± 10.3% (n=200) in men taking the same dose ($p<0.046$). The study authors also noted that a pooled analysis, Stein (1999), had revealed that the greatest efficacy was seen in elderly women taking cerivastatin 400mcg/day who had a mean LDL-C decrease of 40.4% from baseline.

The Panel noted that Stein (1999) was a pooled efficacy analysis of six double-blind randomised placebo controlled or comparative clinical trials where patients with primary hyperlipidaemia had received cerivastatin 100 to 400mcg/day. Primary hyperlipidaemia was defined as plasma LDL-cholesterol levels at the last two lead-in visits of ≥4.12mmol/l for patients with no CHD risk factors and ≥3.35mmol/l if they had two or more risk factors. The efficacy analysis was performed at 8 weeks. The study showed that, based on an efficacy population a statistically significant mean percentage decrease in LDL-C of 36.2% (versus baseline) was achieved in patients receiving 400mcg of cerivastatin; a reduction of 38.2% in female patients and 34.9% in male patients. The greatest reduction of 40.4% was seen in elderly females receiving 400mcg/day. The statistical significance of these gender differences was not stated.

The Panel noted Bayer's submission that differences in efficacy were seen due to differences in study design and patient groups. The leavepiece made no mention of the treatment period for the efficacy results. The costs were based on 28 days treatment. The data presented on pages 3 and 4 of the detail aid clearly stated that the data were from a 24 week study. The Panel did not consider that the use of the Ose *et al* data was unreasonable *per se*. It was not inconsistent with the balance of the evidence. No breach of Clause 7.2 of the Code was ruled.

With regard to the figure of 44% for females on page 3 of the detail aid, the Panel noted that this data had been considered in two previous cases, AUTH/970/1/00 and AUTH/972/1/00. The previous cases had concerned a claim in a journal advertisement that 'New Lipobay 400mcg lowers LDL-cholesterol by up to 44%'.

In Case AUTH/970/1/00 the Panel had noted that gender response was neither a primary nor secondary efficacy parameter in the Ose *et al* study. The statistically significant difference in effect between men and women treated with 400mcg cerivastatin had been shown in an exploratory sub-group analysis to assess the possible gender effects and age on LDL-cholesterol changes. In the study discussion the authors stated that cerivastatin 400mcg appeared to be particularly effective for improving the lipid profile of women. In Case AUTH/970/1/00 the Panel had considered that the claim at issue gave the impression that a reduction of 44% in LDL-C could be achieved in the entire patient population. This was not so. The claim had been qualified by reference to a footnote but it was an accepted principle under the Code that a claim could not be so qualified. Further, the Panel did not accept that preceding 44% by 'up to' provided sufficient qualification nor did it negate the overall impression given. The Panel had considered the claim at issue was misleading and ruled a breach of Clause 7.2 of the Code. The ruling had also applied to Case AUTH/972/1/00.

Turning to the case now before it, AUTH/993/3/00, the Panel noted its previous comments regarding the gender response not being a primary nor secondary efficacy parameter. The data was based on an exploratory sub-group analysis in 102 women. The Panel considered that page 3 of the detail aid was misleading in presenting the gender data in the context of a primary end point analysis. A breach of Clause 7.2 of the Code was ruled.

2 Comparison of 400mcg dose of Lipobay with 10mg atorvastatin and 10mg simvastatin

The comparison appeared in the leavepiece whereby the data for 400mcg Lipobay and 10mg atorvastatin were given in black and thus appeared emboldened amongst the other data which were given in blue.

Page 4 of the detail aid gave data with regard to the cholesterol lowering efficacy of Lipobay 400mcg. Page 5 of the detail aid was headed 'Lipid lowering with the three most common statin prescriptions' and 'mean percentage changes from baseline at week 8'. Data for simvastatin 10mg/day, 20mg/day and atorvastatin 10mg/day with respect to total cholesterol, LDL-cholesterol and HDL-cholesterol were given in a table (referenced to Jones *et al* 1998). A separate table headed 'Lipid lowering in 4S' gave the data for simvastatin 20-40mg/day (referenced to the 4S study 1994). Beneath both tables in a small typeface it was stated 'NB Cerivastatin not included in these studies'.

Page 10 of the detail aid was headed 'Monthly cost of treatment'. It included a bar chart showing the costs of 28 days treatment with various statins. Apart from Lipobay which had two columns, one for the cost of the 100mcg, 200mcg and 300mcg dose and one for the cost of the 400mcg dose, each statin (fluvastatin, pravastatin, simvastatin and atorvastatin) had one column depicting the cost of the various doses. The costs were all given in figures. The Lipobay 400mcg column was yellow and headed 'new', all the others were pale blue for the lowest dose and white for the highest dose.

Page 11 of the detail aid referred to Lipobay 400mcg as a 'Simple to use once-daily dosage' and as 'Cost effective'.

COMPLAINT

The complainant alleged that the comparison was inappropriate and misleading. There was no valid rationale explaining the practical benefits to a prescriber for this non-milligram equivalent comparison which compared the lowest starting dose of atorvastatin and the maximum licensed dosage of Lipobay. To provide a comparison on the basis of 'cost per percentage LDL-C reduction' as in the leavepiece without any further qualification was only fair if it compared like with like, either starting doses or maximum licensed doses. The same was true for the comparison drawn in the detail aid where efficacy data was presented for simvastatin and atorvastatin. The latter was misleading as it created the impression that the data represented the results of head-to-head comparisons with Lipobay 400mcg. Further, even the inclusion of an 'NB' in very small font that 'Cerivastatin not included in these studies' did not help as it was not clear which studies this 'NB' was referring to. In fact, what was the relevance of referring to the Jones and 4S studies? Results from these studies were incomparable as the studies differed in many design parameters to that cited for Lipobay 400mcg (Ose *et al*), not least in terms of the duration over which efficacy was measured, Jones 8 weeks and Ose 24 weeks.

The complainant believed that the style and manner in which this comparison was presented would mislead physicians to believe that lipid lowering therapy could be initiated at the 400mcg dose of Lipobay obviating the need to initiate treatment with Lipobay 100mcg, the licensed starting dosage. The latter false impression was particularly apparent in the hospital detail aid where monthly cost of treatment was shown. Why was the cost of Lipobay 400mcg depicted as a separate prominent yellow bar on page 10 and the cost of the other doses of Lipobay, and that of the other statins, on single less prominent bars? Would it not be much fairer to depict the cost of the maximum licensed doses of the other statins along the same lines as that for the 400mcg dose? Further, on page 11 the detail aid referred to Lipobay 400mcg as being 'Cost effective'. This was meaningless without a clear definition. Clearly there were other measures of cost effectiveness over and above absolute medicine cost. The cost effective claim, arguably, referred to monthly cost. However, if that were so, then to discuss absolute monthly costs without addressing the costs incurred by the specified titration schedule for Lipobay (from 100mcg to 400mcg) misled prescribers by omission and further reinforced the impression that the 400mcg dose was an initiation dose for therapy. The reference to simplicity might be correct in the context of a once daily dosage. However, this claim for simplicity, when considered in the context of the whole item, was misleading as it did not address the issue of a titration schedule which was far from simple and, once again, implied that 400mcg was a recommended starting dose.

RESPONSE

Bayer submitted that clearly a milligram equivalent comparison of the currently marketed statins with Lipobay was irrational based on the microgram dosage of Lipobay. The underlying principle for the comparisons was that of efficacy. Hence the comparison of Lipobay 400mcg with atorvastatin 10mg in the leavepiece since these two products had a very similar efficacy profile in that they both reduced LDL-C by approximately 38%. On this basis the benefit to the prescriber was clear ie one of cost-effectiveness based on cost per percentage LDL-C reduction.

With regard to the points raised concerning the comparisons made in the detail aid, Bayer submitted that the complainant had misunderstood the data presented. The effects of simvastatin 10mg and 20mg and atorvastatin 10mg on lipid parameters found in the Jones study were presented as these were the three most commonly prescribed statins in the UK as stated in the title on this page. This was further qualified by the subheading that stated the source of this data regarding GP prescribing. This was then followed by details of the changes in lipid parameters observed in the 4S study with simvastatin. The findings of these studies had been included as they were regarded as fair representations of the lipid-lowering efficacy of the commonly prescribed doses of these statins. The complainant alleged that the first comparison was misleading as it created the impression that these data represented the results of head-to-head comparisons with Lipobay 400mcg. Surely if this were a head-to-head comparison with Lipobay 400mcg then it would be counterproductive not to present the results obtained for Lipobay. The 'NB Cerivastatin not included in these studies' quite clearly referred to the only two studies referenced on this page namely the Jones and 4S studies. The complainant had not understood the plural nature of the wording used ('these') as no other studies were mentioned on this page. Furthermore, the complainant alleged that the style and manner in which the comparison was presented would mislead physicians to believe that lipid lowering therapy could be initiated at the 400mcg dose of Lipobay without further justification as to why this might be so. No claim was made that therapy could be initiated at Lipobay 400mcg.

Bayer stated that on page 10 of the detail aid the cost of Lipobay 400mcg was depicted as a separate yellow bar as this was the newly licensed dosage for Lipobay and due to the price of 400mcg (£17.35) compared with that of Lipobay 300mcg (£18.20), a separate bar was the most appropriate method to convey this information. No other statin had a similar pricing structure. Depicting the cost of the maximum licensed doses of the other statins along the same lines as that for Lipobay 400mcg would only further highlight the clear monthly cost differences between the statins. The bar chart was a fair comparison since all doses of all statins were included.

Bayer stated that the reference to Lipobay 400mcg as cost effective was within the context of the bar chart depicting the monthly cost of treatment. Cost effectiveness was a relative term based on a ratio for

ranking alternatives. However, the term 'cost effective' was not by definition an economic term, rather it was a reasonable statement given its present context. Given the documented effectiveness of Lipobay, it was reasonable to draw attention to price since cost impact was of immediate relevance and concern to prescribers. In particular, since statin therapy was likely to be lifelong, cost implication to the NHS was an important parameter for physicians to be aware of. In this context the costs of dose titration were likely to be variable based on individual patient characteristics such as the need for titration as well as local costs of lipid profiles and healthcare professional resource. Hence these were much more difficult to quantify, whilst medicine costs were more likely to be absolute. As already stated due to the long-term nature of therapy with statins, costs were very important, whilst those costs relating to dose titration were likely to be insignificant when compared to total costs relating to chronic therapy. Hence the claim that Lipobay was cost-effective. The mere fact that the costs of the other doses of Lipobay were also presented in the bar chart clearly contradicted the complainant's view that this reinforced the impression that 400mcg was an initiation dose for therapy.

Furthermore, the prescribing information clearly stated that Lipobay therapy should be started at 100mcg and titrated if necessary by 100mcg depending on response at four week intervals. The reference to simplicity was justified by the once daily dosage statement. It was clear that the reference to simplicity related only to the once daily dosing and no more and was not misleading.

PANEL RULING

The Panel did not consider that the comparison of cerivastatin 400mcg per day and atorvastatin 10mg per day in the leavepiece was misleading as alleged. The Panel accepted the submission that the comparison was based on efficacy. Data had been given for each dose. It would be inappropriate to compare on a mg for mg basis. As the leavepiece listed all the doses of cerivastatin and atorvastatin readers would be aware that 400mcg was the highest recommended dose of cerivastatin and 10mg was the lowest recommended dose of atorvastatin. No breach of Clause 7.2 of the Code was ruled in this regard.

With regard to page 5 of the detail aid, the Panel did not accept that the impression was given that the data came from a head to head study with Lipobay. The heading clearly referred to the three most common statin prescriptions. The data was referenced to Jones *et al*. No breach of Clause 7.2 was ruled in that regard. The Panel noted that the layout of the two pages was such that the Lipobay data on page 4 would be compared with the data on page 5. The Panel noted that there were differences between the studies and queried whether the data was directly comparable. The Ose *et al* study was for treatment of 24 weeks whereas the Jones study was for 8 weeks. The Panel noted the details of the Ose study (as above). The Jones *et al* (1998) study compared atorvastatin 10, 20, 40, 80mg, simvastatin 10, 20 and 40mg, pravastatin 10, 20 and 40mg, lovastatin 20, 40 and 80mg and fluvastatin 20 and 40 mg in an 8 week study. Patients with hypercholesterolaemia were enrolled with plasma LDL-cholesterol ≥4.2mmol/l. The lengths of the studies were clearly stated but nevertheless the Panel considered that the juxtapositioning of the data was unfair. The Panel noted that the Stein study lasted for 8 weeks and gave lower results for cerivastatin 400mcg than the 24 week data cited. There were differences between the studies. The Panel ruled a breach of Clause 7.2 of the Code in this regard. This ruling also applied to the leavepiece.

The Panel noted that it had already made a general ruling in point 1 above in relation to the need to refer to the starting dose and titration of Lipobay in the detail aid.

The Panel did not consider that it was unfair to use a different colour for the column showing the cost of the 400mcg dose of Lipobay. All the information was presented for the other doses of Lipobay. It was unusual in that the cost of Lipobay 400mcg (£17.35) was the same as the cost of 200mcg, whereas 300mcg was more expensive at £18.20. The Panel ruled no breach of Clause 7.2 of the Code.

The Panel did not accept Bayer's submission with regard to the claim that Lipobay was cost effective. The supplementary information to Clause 7.2 stated that care must be taken that any claim involving the economic evaluation of medicine was borne out by the data and did not exaggerate its significance. In the Panel's view claims for cost effectiveness had to be related to the cost of treatment in general, not just the cost of the medicine. No data had been provided in relation to the economic evaluation of the effectiveness of Lipobay 400mcg. The term 'cost effective' was interpreted as being more than that a product was less expensive than competitor products and it worked. The Panel ruled that the use of the term 'cost effective' in the detail aid was misleading in breach of Clause 7.2 of the Code.

With regard to the claim 'Simple to use once-daily dosage' the Panel noted that whatever the dose of Lipobay, 100mcg, 200mcg, 300mcg or 400mcg, it was a once-daily dosage even during the titration period. The Panel did not consider that the claim was misleading even when it was considered in the context of the whole item. The Panel did not consider that the titration schedule was far from simple as alleged. No breach of Clause 7.2 of the Code was ruled.

APPEAL BY BAYER

Bayer acknowledged that there were differences in the studies by Ose *et al* and Jones *et al* in terms of the duration of therapy. Accordingly, the company clearly cited each representation of data with a separate and distinct reference, and did not accept that a physician would be confused by the presentation of information in this way or that this was an unfair representation of information. It was very clear that different studies were used as source material for these figures.

The specific data relating to Lipobay 400mcg were derived from the Ose *et al* study which was the largest

published study in terms of patient numbers. This was the company's rationale for citing it. The Panel had acknowledged that it considered the Ose *et al* data not unreasonable *per se* having considered other data provided by the company.

With regard to the Jones *et al* (CURVES) study, this study was the only published study evaluating the efficacy of all doses of all available statins marketed at the time the study was conducted. This excluded Lipobay, fluvastatin 80mg and simvastatin 80mg, which became available after completion of the study. Despite these omissions it remained the most comprehensive and therefore appropriate data to cite. It was widely used by other statin manufacturers. In addition, the patient demographics and selection criteria were similar to the those of the Ose *et al* study.

Bayer stated that its review of the published literature for the various statins revealed that the LDL-cholesterol reductions seen in the CURVES study were representative of the body of evidence for these statins. Furthermore, the SPC for each statin stated that the maximal LDL-cholesterol lowering effects were seen after 4 weeks of therapy. Hence, the differences in duration of treatment between Ose and Jones were not clinically relevant. The company therefore considered that this extrapolation was a fair one and one that physicians would find of particular relevance.

Further, Bayer was aware that other statin manufacturers, in the absence of published trials comparing all statins, depicted data in this manner. An example of this was provided.

APPEAL BOARD RULING

The Appeal Board noted that there were differences in the studies by Ose *et al* and Jones *et al* in terms of duration of therapy (24 weeks and 8 weeks respectively). However, given that the therapeutic response to statins was seen within 4-6 weeks of therapy, and the response was maintained during continuation of therapy, the difference in duration of therapy between the two studies would make no clinical difference with regard to lipid lowering effect. The detail aid referred to the relevant time periods.

The Appeal Board noted that the detail aid was primarily aimed at hospital doctors. This was a specialist audience and one that was interested in targets with regard to percentage lowering of cholesterol. The pages in question showed what doses of cerivastatin, simvastatin, and atorvastatin should be used to achieve a target reduction of about 25% in total cholesterol. Readers would relate the doses shown to a target reduction in cholesterol.

The Appeal Board did not consider that presentation of the data on pages 4 and 5 was unfair or misleading. No breach of Clause 7.2 was ruled. This ruling also applied to the leavepiece. The appeal was successful.

3 Prescribing information

COMPLAINT

The complainant stated that the prescribing information in both items outlined, albeit in very small and difficult to read font, the titration schedules. However the complainant believed that for many prescribers the manner in which the prescribing information was presented, alongside all the other claims for Lipobay 400mcg, created the impression that the 400mcg dosage was a stand alone dosage and that prescribers might not be required to follow the recommended titration schedule for Lipobay. This was further reinforced by the actual prescribing information provided. The latter was specific to the 400mcg dosage as seen in the title to the prescribing information section. Bayer had a separate SPC for the 100mcg, 200mcg and 300mcg dosages. This fact, and a clarification that the prescribing information was identical for all licensed doses of Lipobay, should be stated in the item in order not to create the false impression that the prescribing information relevant to the 400mcg dose was somehow different to that of the other doses of Lipobay.

RESPONSE

Bayer stated that the prescribing information in both items conformed to the Code, hence the comments regarding size of font were unnecessary and irrelevant. The complainant did not state reasons as to why the manner in which the prescribing information was presented created the impression that the 400mcg dosage was a stand alone dosage and that prescribers might not be required to follow the titration schedule. In no part of the items in question was there any statement to this effect. Clearly the focus of the materials was on the 400mcg dose since this was the newly launched dosage for Lipobay. Since there were separate SPCs for Lipobay 400mcg and the 100-300mcg doses, that which was most relevant to the data presented in the promotional items was presented, namely the SPC for Lipobay 400mcg. This was clearly stated in the title, however as stated by the complainant the content of this document was identical to that of the SPC for Lipobay 100-300mcg. It was difficult to conceive how the lack of a statement to the effect the prescribing information was identical for all licensed doses created a false impression that the prescribing information for Lipobay 400mcg was somehow different to that of the other doses without further explanation by the complainant. In addition, the SPC for Lipobay 400mcg was the only one to contain information on all doses.

PANEL RULING

The Panel did not consider that the prescribing information was difficult to read in either the leavepiece or the detail aid. The supplementary information to Clause 4.1 of the Code recommended that a lower case 'x' was no less than 1mm in height. Both items met that requirement. The line length and the spacing between the lines was not unreasonable. The Panel ruled no breach of Clause 4.1 of the Code.

The Panel noted that it had already made some comments about the prescribing information in point 1 above. The Panel noted that both items included only the prescribing information for the 400mcg dose. In the Panel's view both items promoted all four

doses of Lipobay and the prescribing information for all doses should have been provided. The indications etc were the same for all the doses but of course other elements of the prescribing information were not the same for all the doses. For example the costs of the 100mcg, 200mcg and 300mcg doses had not been given nor had the product licence numbers. The Panel therefore ruled a breach of Clause 4.1 in this regard.

4 Safety profile and ongoing research

Page 7 of the detail aid headed 'cerivastatin 400mcg side-effect profile' stated that '… cerivastatin has an exceptionally good safety profile …' and also that 'In contrast to existing statins, there was no evidence of any dose related increase in adverse effects with cerivastatin'. Both statements were quotations.

Page 13 of the detail aid referred to the risk evaluation and stroke prevention in the elderly – cerivastatin trial – the RESPECT study. The study endpoints were given as first stroke event, first cardiac event, first stroke or cardiac event.

The detail aid referred to two other studies. Page 15 of the detail aid stated that research was continuing on the pleiotropic effects of cerivastatin.

COMPLAINT

The complainant queried why the cerivastatin safety profile was exceptional. All statins offered an adverse effect profile that was comparable to placebo. In the complainant's opinion a 'new' dosage offered no unique advantages in terms of 'safety' over other established products in this class. The safety of Lipobay 400mcg could only be assured after a significant period of post-marketing surveillance and in this context the claim was clearly an exaggeration. Further, to suggest that 'In contrast to existing statins there was no evidence of any dose related increase in adverse effects with cerivastatin' was false and misleading and disparaging of the other statins. The latter claim was also referenced to the Stein (1998) study. This was not a comparative study including all existing statins. Further, the study was not powered to investigate safety as the primary efficacy parameter. To suggest otherwise was an exaggeration. This inappropriate and misleading use of study data by Bayer in promotional materials was further exemplified by the reference on page 13 of the detail aid to the RESPECT study. The impression that this page created was that the study had completed and Lipobay 400mcg was licensed for the endpoints investigated. This impression was further strengthened by the fact that with regard to the other studies also described, there was a clear statement that these were ongoing with the year in which results were expected clearly stated. The same could be said of the page referring to the pleiotropic effects of cerivastatin. There was no clarification that these were not effects for which Lipobay had a licence. In fact, a number of the other statins had, arguably, a superior pleiotropic effects profile compared to Lipobay, however none of these were promoted on the basis of these effects. Why should Lipobay be different? The complainant suggested that there were not any robust clinically relevant human data available.

RESPONSE

Bayer stated that both statements on page 7 were clearly referenced as quotes from a publication by Stein (1998) where the incidence of adverse events with cerivastatin was found to be comparable to that observed with placebo. From this it could be said that Lipobay 400mcg was well-tolerated and had a good safety profile. The statement 'In contrast to existing statins there was no evidence of any dose related increase in adverse effects with cerivastatin' was not misleading, rather it was stating the opinion of the author who was a well-respected lipid specialist. It was not disparaging of other statins as there was evidence that adverse effects such as persistent elevations in liver enzymes occurred more frequently with higher doses of other statins (eg atorvastatin). The complainant stated correctly that this was not a comparative study nor was it powered to investigate safety as the primary efficacy parameter, however no claims of statistically significant superiority with respect to safety were made, hence this statement was clearly not an exaggeration and was valid in the context which it was used.

In Bayer's view the complainant's points relating to the RESPECT study were inappropriate. The tab indexing the pages of the hospital detail aid clearly stated 'Ongoing Trials', hence this clearly contradicted the complainant's view that this page created an impression that the study was completed. Furthermore all sentences on this page were in the future tense, no results were presented and use of words such as 'planned', 'will' and 'until' all reinforced the message that the study was ongoing. Similarly the section describing the pleiotropic effects of cerivastatin was entitled 'Ongoing Trials'. This was simply a description of ongoing research areas with no suggestion that Lipobay had a licence in these areas. On the contrary the headings for each pleiotropic effect were descriptive in their nature (eg 'Effects on intimal thickening'). A licence claim would describe the benefit of Lipobay in each of these areas (eg 'Inhibition of intimal thickening') which was not the case. This page was aimed at specialists for academic and scientific interest. The complainant stated that other statins had arguably a superior pleiotropic effects profile, but no evidence was provided. In response to the complainant's question 'Why should Lipobay be different?', there was no claim that Lipobay was different. The complainant's question 'Were there any robust clinically relevant human data available?' demonstrated a lack of awareness of the pleiotropic effects area since very little or no human data were available. At present it was not possible to measure the effects of statins on vascular smooth muscle cell growth in humans. Data relating to ongoing trials such as RESPECT and pleiotropic effects was often requested by specialists, hence the intention of these pages was to provide this information and not to promote unlicensed indications.

PANEL RULING

The Panel noted that Stein *et al* (1998) was a global pooled analysis of the efficacy, safety and tolerability of cerivastatin. The study stated that the product was

well tolerated with the type and incidence of clinical adverse effects comparable to that of placebo and comparator products. The study concluded that 'Based on the pooled safety analysis, cerivastatin has an exceptionally good safety profile with an incidence of adverse effects comparable to placebo. In contrast to existing statins there was no evidence of any dose related increase in adverse effects with cerivastatin.' The analysis of the ten most frequently reported adverse events showed no significant differences in incidence rates between treatment with cerivastatin with either placebo or active comparators. Similarly there was no significant difference between cerivastatin at any dose, placebo and active comparator in the incidence of adverse effects that were attributed to study treatment.

The Panel noted that the first quotation from the Stein study given in the detail aid was accurate. The long-term safety was assessed in patients who were randomised to receive any dose of cerivastatin during either double-blind controlled efficacy periods of 4-32 weeks or double-blind placebo controlled efficacy periods of 4-24 weeks. The data was from Phase II and III clinical trials. The Panel noted that the study was from a pooled analysis and was not powered to investigate safety as the primary efficacy parameter. It was not a comparative study as such. The Panel considered that the quotation implied that cerivastatin had an excellent safety profile. The Panel considered that it was misleading to use the quotation given the data that it was based on and a breach of Clause 7.2 of the Code was ruled.

The Panel considered that the quotation 'In contrast to existing statins there was no evidence of any dose related increase in adverse events with cerivastatin' was an accurate quotation from Stein (1998) data. The Panel noted that the Ose *et al* study stated that the incidence of adverse events considered to have a possible or probable relationship to cerivastatin therapy were comparable in the 400mcg dose group and the 200mcg dose group. The Bayer data on file – Third Addendum to Clinical Expert Report – stated that certain adverse events appeared at peak incidence in the 400mcg dosage group and that even this peak incidence was not a cause of clinical concern; no events had been seen which might be unexpected for statins as a class and all had previously been recorded for cerivastatin during clinical development of the lower doses. The only event that might be considered dose related was asthenia.

The Panel considered that it was misleading to state that there was no evidence of any dose related increase in adverse events based on the Stein (1998) data. Other data was not so unequivocal. The Panel considered that the quotation was not a balanced reflection of all the data. A breach of Clause 7.2 of the Code was ruled.

With regard to the section on ongoing trials (pages 12, 13, 14 and 15 of the detail aid), the Panel was concerned that this section might imply that Lipobay was licensed for the endpoints used in the trials and the doses used. With regard to the RESPECT study the Panel noted that the detail aid indicated by use of an asterisk that one of the doses, 800mcg was not licensed. The Panel accepted that health professionals would be interested in ongoing research. It was not appropriate for details of ongoing research to be given in promotional material if the research related to unlicensed indications and doses. The Panel considered that pages 12, 13, 14 and 15 in effect amounted to promotion of unlicensed indications and/or doses. The tabs on the pages, although labelled 'Ongoing Trials', did not negate this impression. A breach of Clause 3.2 of the Code was ruled.

APPEAL BY BAYER

Bayer stated that it wished to appeal against the Panel's decision regarding the alleged breach of Clause 3.2 of the Code concerning the section on ongoing trials (pages 12, 13, 14 and 15 of the detail aid). The company considered it wholly appropriate to include ongoing clinical research in its detail aid. These trials had been described in order to inform physicians working in this therapeutic area who were genuinely interested in, and regularly asked for information relating to, ongoing research. The detail aid in question was for use in hospitals and the inclusion of ongoing research was of particular relevance to this target audience. Hospital physicians working in this therapeutic area were very familiar with the licensed indications of Lipobay. The company could not accept that these pages implied that Lipobay was licensed for any indication other than the treatment of hypercholesterolaemia or that doses greater than 400mcg should be used. They presented a simple summary of ongoing trial work.

Bayer further stated that it was an accepted practice within the pharmaceutical industry to include such ongoing trial data in detail aids and other information items. For example, Pfizer and Parke Davis's detail aid contained information on the ongoing trials MIRACL, CARDS and TNT. End-points were described for each of these studies for which atorvastatin was not licensed. The company was also aware that Pfizer and Parke Davis's electronic detail aid contained information on ongoing clinical work. Again, Bayer stated that it cited this item purely for information purposes.

The company representatives said that the format of the information on ongoing research had been changed in the new detail aid.

APPEAL BOARD RULING

The Appeal Board noted that the detail aid in question was aimed primarily at hospital doctors, a group that was keen to receive evidence based data and to know what other data was being looked for in on-going trials.

The Appeal Board noted that pages 12-14 of the detail aid presented the key points about the design and objectives of four ongoing trials. The details for three of the trials clearly included the year in which the results were expected. With regard to a fourth trial it was stated that the minimum planned treatment time was 4 years per patient or until 518 strokes had been observed. No results for any of the trials were given and in the Appeal Board's view no claims for Lipobay were made. Page 15 listed the key areas involved in

published and ongoing trials. The Appeal Board was concerned about the layout of the pages in question. Noting that the intended audience was specialists, the Appeal Board decided that on balance the pages 12-15 did not promote Lipobay outside the terms of its licence. The Appeal Board ruled no breach of Clause 3.2. The appeal was successful.

5 Interactions

Pages 8 and 9 of the detail aid referred to drug interactions and metabolism of cerivastatin. Page 8 included a table comparing cerivastatin, simvastatin and atorvastatin with regard to interactions with digoxin and warfarin. Ticks and crosses were used to show that cerivastatin had no interactions with digoxin and warfarin unlike simvastatin and atorvastatin.

Page 9 included two diagrams showing the metabolism of cerivastatin by cytochrome P450. The first diagram related to monotherapy and showed that cerivastatin was metabolised by CYP3A4 and CYP2C8. The second diagram showed the effect that a CYP3A4 blocker, in this instance erythromycin, had. The second diagram showed that the CYP3A4 pathway was blocked and increased metabolism of cerivastatin by the CYP2C8 pathway.

Page 8 also stated that cerivastatin did not influence cyclosporin blood trough levels unlike atorvastatin which had been shown to raise cyclosporin blood levels in some patients by more than 25%.

COMPLAINT

The complainant alleged that a fundamental tenet of pharmacology and therapeutics was confused and distorted to suit a marketing strategy that misled the prescriber. Page 9 of the detail aid depicted that Lipobay was metabolised by the CYP 3A4 and 2C8 isoenzymes. This would therefore suggest that Lipobay in fact did bind to the CYP 34A isoenzyme. However, on the preceding page entitled 'Drug interactions profile' there appeared to be an unequivocal statement that Lipobay had no interactions with digoxin and warfarin. Metabolism of the latter products was associated with the CYP 3A4 isoenzyme and therefore assumed that these medicines bound to the CYP 3A4 isoenzyme. The Lipobay SPC might refer to the wording 'no interactions' however this did not detract from the basic fact that if two medicines bound, reversibly or irreversibly and to a varying or similar extent, to a common receptor, then there always remained the potential for an interaction. This interaction might or might not be clinically significant but nevertheless the potential for interactions was always there. Thus the categorical nature of the claim for Lipobay and its depiction with ticks and crosses was an exaggeration of the facts. A qualification was required in order to avoid confusion.

Page 8 also referred to cyclosporin blood trough levels. There was a clear and misleading suggestion that Lipobay did not interact with cyclosporin and that there was robust evidence to support this. This was simply not true. Further, in this regard the comparison was made with atorvastatin however would it not also be appropriate to include simvastatin in order to deliver a balanced comparison, particularly as both statins were compared in the section immediately above? The misleading impression created was that both Lipobay and simvastatin did not interact with cyclosporin.

RESPONSE

Bayer accepted the complainant's points regarding the binding of Lipobay to the CYP 3A4 isoenzyme. However accepting that there might be a theoretical possibility of an interaction between Lipobay and warfarin, this had not been shown to be the case in a clinical trial. A further trial investigating the possibility of an interaction between Lipobay and digoxin had also confirmed no interaction. The results of these trials had been accepted by the MCA and formed part of the marketing authorisation, hence the wording in the SPC of no interaction. In comparison the SPCs for atorvastatin and simvastatin informed prescribers of the potential for interaction when digoxin/warfarin were co-prescribed with either of these statins and recommendations for monitoring were made where appropriate. The table outlining these facts was therefore not an exaggeration, rather a guide to prescribers. The statements describing the effects of Lipobay and atorvastatin on cyclosporin blood trough levels were reporting the results of a comparative trial in which the two medicines in question were included. The statements made were specific to the effect of each statin on cyclosporin blood trough levels and did not claim that Lipobay did not interact with cyclosporin at all. Simvastatin was not included in these comparisons, as were none of the other statins, as it was not investigated in this study.

PANEL RULING

The Panel noted that the Lipobay 400mcg SPC stated that cerivastatin was metabolised via a dual metabolic pathway utilising at least two cytochrome P450 isoenzymes, CYP2C8 and CYP3A4. A compensatory effect might be observed when one pathway was inhibited. The SPC also stated that based on *in vitro* enzyme affinity investigations there was no evidence of any cytochrome P450 inhibitory potential of cerivastatin including the major drug metabolizing enzyme CYP3A4. As expected from these findings no interaction with other co-medicated drugs which were substrates of CYP3A4 or other CYP enzymes were observed *in vivo*. The SPC said that co administration of a single dose of warfarin to healthy subjects who had received Lipobay 300mcg for seven days did not result in any changes in prothrombin time or clotting factor VII activity when compared with placebo. The pharmacokinetics of both warfarin isomers were unaffected by concomitant administration of 300mcg Lipobay. The SPC also stated that plasma digoxin levels and digoxin clearance at steady state were not affected by concomitant administration of Lipobay 200mcg.

The Panel noted the submission from Bayer that, accepting that there might be a theoretical possibility of an interaction between Lipobay and warfarin, this had not been shown to be so in a clinical trial (Schall

et al (1995) on 21 male volunteers). The Panel considered that given the data in the SPC it was not unacceptable to state there were no interactions between warfarin and cerivastatin and digoxin and cerivastatin. No breach of Clause 7.2 of the Code was ruled in this regard.

The cyclosporin data was referenced to an abstract by Renders *et al* (1998) which concluded that cerivastatin seemed not to influence cyclosporin A blood trough levels whereas atorvastatin did increase levels in a considerable portion of the patients. Ten patients were treated with cerivastatin 200mcg, ten patients were treated with atorvastatin 10mg and ten patients were assigned to the control group. The reason for the side-effect was unknown but might be due to drug interaction via the cytochrome P450 enzyme system. The Panel considered that the detail aid was not a fair reflection of the results in the small study of 30 patients. The abstract used the description 'seemed not to influence' where as the detail aid stated 'does not influence'. The Panel ruled a breach of Clause 7.2 of the Code.

Complaint received **29 March 2000**

Case completed **15 August 2000**

CASE AUTH/1008/4/00

SMITHKLINE BEECHAM v AVENTIS PASTEUR MSD

'Dear Healthcare Professional' letter about Avaxim

SmithKline Beecham complained about a letter which Aventis Pasteur MSD had sent to all general practitioners and practice nurses in the UK and had provided to its sales representatives. The letter stated that it was sent in response to a number of enquiries about the needle length used for its adult hepatitis A vaccine, Avaxim, and stated that the main concern had been that the 16mm, 25 gauge needle used was not reaching the deltoid muscle, thus compromising seroconversion, and that the company had been told that the anxiety had been prompted by an arm model demonstration by another vaccine company. The letter stated that this entirely theoretical suggestion was completely negated by available immunogenicity and safety data. A table favourably comparing the percentage of local reactions and seroconversion rates obtained with Avaxim with those observed with the SmithKline Beecham hepatitis A vaccine was included in the letter as was a second table which stated the seroconversion rates at weeks 0, 4, 24 and 28 obtained with the intramuscular, needle-less jet and subcutaneous administration of Avaxim.

SmithKline Beecham stated that the reference to anxiety arising from an arm model demonstration by another vaccine company was a clear reference to SmithKline Beecham which had not at any time made such an allegation and this was alleged to be disparaging. The Panel noted that SmithKline Beecham had used a fat arm model and considered that this had led health professionals to contact Aventis Pasteur MSD about the needle length of Avaxim. In the circumstances the Panel did not think that the reference was disparaging to SmithKline Beecham as alleged and no breach was ruled.

The letter included the claim that Avaxim produced fewer local adverse reactions and faster seroconversion than the hepatitis A vaccine to which it was compared (SmithKline Beecham's Havrix Monodose). SmithKline Beecham alleged that the study upon which this was based was flawed and the inferences drawn did not reflect the full literature or the summaries of product characteristics (SPCs). On balance the Panel considered the data in the letter concerning seroconversion was not misleading and ruled no breach of the Code. The Panel was concerned that the letter did not fairly reflect the situation regarding local adverse reactions. The data was more limited. On balance the Panel decided that the letter was misleading in this regard and a breach of the Code was ruled.

SmithKline Beecham stated that the letter drew attention to the 25 gauge needle used for Avaxim. This was not the recommended choice for adult administration of intramuscular vaccines. The Panel noted that Avaxim used a 25 gauge needle which was attached to the syringe and could not be changed. The vaccine, syringe and needle were licensed as a complete entity. Thus querying the needle size in effect queried the basis for the licence. It was thus acceptable for the letter to refer to the 25 gauge needle used for Avaxim. No breach of the Code was ruled.

SmithKline Beecham pointed out that the letter then presented data for Avaxim outside the licensed indication to support the view that however given Avaxim was immunogenic. It did not however give any indication as to the tolerability of the different delivery mechanisms. If tolerability was seen as so important in the earlier part of the letter why was this not given here. This was a serious deficiency and in SmithKline Beecham's view made the letter unbalanced. Nor did it give any indication of the

number of patients involved. The Panel considered the data presented on the immunogenicity obtained with Avaxim using three different routes of administration; intramuscular, jet and subcutaneously. The data had probably been included to answer the concerns raised by SmithKline Beecham and to reassure healthcare professionals that seroconversion occurred even if Avaxim 'missed' the muscle. The phrase 'It is important to stress that Avaxim is only licensed to be given intramuscularly' introduced the relevant section. The Panel noted the wording of the Avaxim SPC, in particular the need to inject via the intramuscular route in order to minimise local reactions and the reference to use of the subcutaneous route in exceptional circumstances. The Panel considered that the letter was misleading and a breach of the Code was ruled.

The Panel did not consider that the letter brought discredit upon or reduced confidence in the pharmaceutical industry, as had been alleged, and ruled no breach of the Code in that regard.

SmithKline Beecham Pharmaceuticals complained about a 'Dear Healthcare Professional' letter (ref: RA237/0200) which had been sent to all general practitioners and practice nurses in the UK by Aventis Pasteur MSD Ltd and provided to its sales representatives.

The letter, signed by the medical director of Aventis Pasteur MSD, stated that it was sent in response to a number of enquiries about the needle length used for its adult hepatitis A vaccine, Avaxim, and sought to reassure the reader that the choice of needle for Avaxim was based on extensive and robust clinical research. The letter stated that the main concern had been that the 16mm, 25 gauge needle used on Avaxim was not reaching the deltoid muscle thus compromising seroconversion and that the company had been told that this anxiety had been prompted by an arm model demonstration by another vaccine company. The letter stated that this entirely theoretical suggestion was completely negated by available immunogenicity and safety data. A table favourably comparing the percentage of local reactions and seroconversion rates obtained with Avaxim with those observed with the SmithKline Beecham hepatitis A vaccine was included in the letter as was a second table which stated the seroconversion rates at weeks 0, 4, 24 and 28 obtained with the intramuscular, needle-less jet and subcutaneous administration of Avaxim.

Aventis Pasteur MSD provided copies of two further 'Dear Healthcare Professional' letters; the first (ref HEP A/HA003a) was directed at practice nurses whilst the second (ref HEP A/HA003) was addressed to those who had enquired about the Avaxim needle length after an article in the Journal of the American Medical Association (JAMA).

COMPLAINT

SmithKline Beecham alleged that the data included in the letter contained information and claims which were inaccurate, unbalanced, did not reflect currently available evidence and misled in breach of Clause 7.2 of the Code.

The letter stated that Aventis Pasteur MSD had received enquiries regarding the needle length and that Avaxim was 'not reaching the deltoid muscle, thus compromising seroconversion.' It was alleged that this was due to an arm model demonstration by another vaccine company. This was clearly a reference to SmithKline Beecham which had not at any time made such allegations and believed this disparaged it in breach of Clause 8.1 of the Code.

Data was presented in the letter which referred to a clinical paper (Zuckerman *et al* 1997) and included the claim that Avaxim produced fewer local adverse reactions and faster seroconversion than the hepatitis A vaccine (SmithKline Beecham's Havrix Monodose) to which it was compared. SmithKline Beecham believed this study had several flaws and the inferences drawn did not reflect the full literature or indeed the summaries of product characteristics (SPCs) of Avaxim or Havrix Monodose. Antibody titres for Havrix Monodose were normally measured using an enzyme linked immuno-sorbent assay (ELISA), not a radioimmuno assay (RIA) as used for Avaxim and in this trial. For this reason there was an inherent bias towards Avaxim as a preferred assay, RIA, was used. A fairer comparison would have been to have used both the ELISA and RIA methods.

Nevertheless, in another study by Victor *et al* (1994) the RIA method was used to measure antibody level for Havrix Monodose; results of which were 96% seroconversion at 2 weeks. So despite the method used an excellent seroconversion rate was demonstrated. This illustrated the point that the same test conducted by different investigators could give different results. The results of the paper by Zuckerman had not been duplicated by other investigators.

SmithKline Beecham pointed out that the Avaxim SPC stated that 14 days after vaccination more than 90% of immunocompetent subjects were protected. This was comparable to that worded on Havrix Monodose SPC whereby specific humoral antibodies against hepatitis A virus (HAV) were detected in more than 88% of vaccinees on day 15 and corresponded with the SmithKline Beecham clinical trials on Havrix Monodose.

Zuckerman *et al* being an open trial allowed both the patient and nurse to see which vaccine was being used ie Avaxim was 0.5ml and had a smaller (5/8") needle. Such conditions could not allow completely unbiased reporting of adverse events, and therefore cast a degree of doubt over results pooled. In addition, the study did not assess pain. In another vaccine trial with diphtheria/tetanus/pertussis-polio (DTP-polio) vaccine, Ipp *et al* (1989), a longer 1" needle was less painful than a 5/8" needle.

SmithKline Beecham stated that the local reactions data quoted prominently in the letter were for 'after 1st dose in seronegative subjects'. Why was this selective population chosen? Data was different for the seropositive subjects and did not reach significance either for immediate, local or systemic reactions. Differences seen were also considerably lower for booster doses however the highest possible differences were displayed. The discussion in the

paper commented that both vaccines had a good safety profile, with slightly better local reactogenicity results observed for Avaxim. This was not in keeping with the tone of the letter or the prominence given to the claim.

It was also worth noting that the letter drew attention to the 25 gauge needle used for Avaxim. This gauge of needle was not the recommended choice for adult administration of intramuscular vaccines (Department of Health 1996 Immunisation again Infectious Disease-published by HMSO).

SmithKline Beecham pointed out that the letter then presented data for Avaxim outside the licensed indication to support the view that however given Avaxim was immunogenic. It did not however give any indication as to the tolerability of the different delivery mechanisms, if tolerability was seen as so important in the earlier part of the letter why was this not given here. This was a serious deficiency and in SmithKline Beecham's view made the letter unbalanced. Nor did it give any indication of the number of patients involved.

Overall SmithKline Beecham believed this letter was flawed, unbalanced, did not reflect data in the Havrix Monodose SPC, gave undue prominence to local reaction data in breach of Clause 7.2 and further disparaged Havrix Monodose in breach of Clause 8.1.

Because of the authority of the author of the letter and the wide dissemination of this information SmithKline Beecham believed this letter bought discredit upon and reduced confidence in the pharmaceutical industry in breach of Clause 2.

RESPONSE

Aventis Pasteur MSD stated that during the last quarter of 1999 it received a number of reports from its sales force that SmithKline Beecham sales representatives were using a model of a human arm, the 'fat-pad arm model', to demonstrate that a 16mm 25 gauge (5/8") needle was inferior to a 25mm 23 gauge (1") needle for intramuscular injections in adults. This model was used to promote SmithKline Beecham products with a 1" needle as likely to produce a better immune response rate than the Aventis Pasteur MSD products which had a fixed 16mm 25 gauge needle. In particular, the immunogenicity and therefore efficacy of Avaxim had been questioned. This campaign was being undertaken in the absence of any data which directly linked needle length and immunogenicity.

These reports were investigated carefully by Aventis Pasteur MSD. The investigation showed that the use of the 'fat-pad arm model' by SmithKline Beecham sales representatives was widespread. It also showed that it was generating widespread concern amongst healthcare professionals about the acceptability of the 16mm 25 gauge needle. This concern and its origin had been highlighted by the number of needle length enquiries from customers to Aventis Pasteur MSD. As a result of this, the company wrote to SmithKline Beecham to express concern at the use of the arm model and pointed out that where a licensed product such as Avaxim had a fixed needle this represented an intrinsic part of the licence, supported by a full dossier of data generated with this needle length. To question the acceptability of the needle length was to question the validity of the product licence itself.

The response from SmithKline Beecham was:

'You raise the question of demonstration of needles and I will provide further guidance to the Sales Force at our conference in January as to what it can and can't do. I think it is a perfectly legitimate activity to discuss the issue of the needle length in relation to adult and paediatric vaccination but this will be done to stress the importance for SmithKline Beecham's products as opposed to any of yours'.

Aventis Pasteur MSD stated that it was difficult to understand how a discussion on needle length by a sales representative could fail to include the question of which needle length was better. Using the 'fat-pad arm model' the implicit, or in many cases explicit, conclusion being promoted by the SmithKline Beecham field force was that its 1" 23 gauge needle was better than the 16mm 25 gauge needle. Regardless of the original intention, this sales tool was presenting an irresistible temptation to the SmithKline Beecham sales representatives to differentiate products on needle size.

In reality the only data which correlated needle length and gauge with immunogenicity and safety was the data included in the product licences for injectable products. In the case of intramuscular injection, because of the morphological heterogenicity of the human race, there was no regulatory requirement to assess the depth to which a needle intended for intramuscular injection had actually penetrated. As a result the product licence was based on the safety and immunogenicity of the product using the licensed needle size and an intention to inject intramuscularly. To question this data was to question the regulatory acceptability of the product concerned.

Despite the further guidance offered to the SmithKline Beecham sales team at the conference Aventis Pasteur MSD continued to receive enquiries generated by the use of the 'fat-pad arm model'. As a result Aventis Pasteur MSD raised the issue once again in a letter to SmithKline Beecham. In this letter to SmithKline Beecham it had attached a copy of the standard response to needle length enquiries generated by the 'fat-pad arm model'.

The response from SmithKline Beecham was:

'With regard to your second point regarding the fat-pad models, the purpose of these models is not in any way to suggest that the basis for your licence for any of your products is unacceptable. We believe that the question of needle length and acceptability for different patient types is a legitimate activity in relation to the selection of which needle to use for SmithKline Beecham's products. Briefing notes to representatives should only use information in relation to our products. If customers make alternative inferences we cannot be held responsible for these.'

Aventis Pasteur MSD stated that this clearly demonstrated that the purpose of the 'fat-pad arm model' was to generate discussion about the suitability of different needle sizes. Once again it was

very difficult to conceive a scenario where a sales representative would restrict this discussion to their product. The 'alternative inferences' drawn by customers were therefore inevitable and the responsibility for such inferences must lie with SmithKline Beecham and the use of the 'fat-pad arm model'. The questions from customers confirmed that such alternative inferences were widespread.

A few days later Aventis Pasteur MSD received a letter from a practice nurse who had attended a SmithKline Beecham study day, questioning the acceptability of the 16mm 25 gauge needle and noted that this was clear confirmation that this activity was institutional. A copy of the letter was provided. This letter was followed by a telephone discussion with SmithKline Beecham in a final attempt to resolve the situation. Despite the letter from the practice nurse, SmithKline Beecham was unwilling to accept that this practice was causing extreme and unwarranted concern amongst Aventis Pasteur MSD's customers.

In light of the letter from the practice nurse, the continuing number of enquiries to its sales force, Vaccine Direct, Vaccine Information Service and medical information teams and SmithKline Beecham's unwillingness to accept responsibility for its actions, Aventis Pasteur MSD was forced to conclude that this practice would continue and that it needed to take immediate action to reassure its concerned customers. The letter at issue was therefore sent to all GPs and practice nurses in the UK on 13 March 2000. Copies were also given to Aventis Pasteur MSD sales representatives.

The purpose of the letter was to balance the activity of the SmithKline Beecham sales force by re-assuring customers that the 16mm 25 gauge needle was able to induce an excellent immune response whilst utilising the minimum necessary needle size in order to minimise patient discomfort.

Aventis Pasteur MSD submitted that the letter from the practice nurse provided clear evidence that it had indeed received many enquiries about the needle length, that SmithKline Beecham itself admitted to using the 'fat-pad arm model' and that this model had been used to disparage Avaxim. This was therefore fact rather than allegation and was not a pretext used to justify the letter that was sent.

Aventis Pasteur MSD stated that the letter referred to two publications The first of the two would be addressed when considering the available comparative data for all inactivated hepatitis A vaccines including Havrix and Avaxim. The second reference was required to address the question raised by the SmithKline Beecham 'fat-pad arm model' namely what could happen if, as a result of someone having a fat arm or through variation in injection technique, Avaxim was inadvertently injected in to the subcutaneous or even more superficial layer of the arm. The conclusion was that, despite the licensed indication to inject intramuscularly, if the vaccine was to end up in a more superficial layer the immune response would not be impaired. This evidence was central to the defence of the unsupported claims being made with the 'fat-pad arm model'. There was no intention to promote outside the licence and the restrictions of the licence were made very clear in the text of the letter and abbreviated prescribing information was printed on the reverse of the letter. Without this data it would have been impossible to have adequately addressed the concerns of healthcare professionals. Section 4.2 of the Avaxim SPC did provide for subcutaneous injection in exceptional circumstances.

The complaint from SmithKline Beecham was that the data used had several flaws and the inferences drawn did not reflect the full literature or indeed the SPCs of Avaxim or Havrix Monodose.

A full literature search showed that, excluding dose finding or pre-licence studies, there had been seven studies in which two inactivated hepatitis A vaccines had been compared. Havrix was included in all of these comparisons but in only four was the current antigen contact vaccine (1440 ELISA UNITS) used. In two of these Havrix was compared to Vaqta and in the other two Havrix was compared to Avaxim (Zuckerman *et al* 1998 and Zuckerman *et al* 1997). This included the reference cited in the letter at issue. Where Havrix was compared to Vaqta the anti-HAV geometric mean titres (GMTs) (mIU/mL) were consistently although not statistically significantly higher for Vaqta than Havrix in both studies. Where tolerability was compared Havrix was associated with significantly more local reactions than Vaqta.

The letter sent to the doctors about needle length concerned Avaxim. In the studies where Havrix and Avaxim were compared the increase in anti-HAV GMTs was significantly greater with Avaxim than Havrix in both studies and there was significantly less local pain with Avaxim than Havrix in both studies.

In summary, the full body of available data demonstrated that Havrix was never better tolerated nor more immunogenic than any other inactivated hepatitis A vaccine to which it had been compared. It also demonstrated that Avaxim was always significantly more immunogenic and better tolerated locally than Havrix in all cases where the two were being compared. Thus the data presented in the letter was an accurate reflection of all currently available evidence which neither misled nor disparaged.

The relevance of this data to the letter to healthcare professionals was that local tolerability was one of the key factors for the choice of the smaller gauge needle. The available data supported this whilst refuting any suggestion that the smaller gauge needle would impair the immune response to Avaxim when there was an intention to inject intramuscularly.

Aventis Pasteur MSD referred to SmithKline Beecham's suggestion that the use of an RIA methodology for hepatitis A virus antibody measurement in all these studies was likely to have introduced an inherent bias towards Avaxim. It had not provided data to support this suggestion and indeed the study that it cited to demonstrate the immunogenicity of Havrix used the RIA methodology. Aventis Pasteur MSD was aware that RIA might give lower GMTs than ELISA for all inactivate hepatitis A vaccines, but it was unaware that use of a RIA methodology inherently favoured Avaxim or indeed any inactivated hepatitis A vaccine

over any other. Finally, it was difficult to see how a non-comparative study such as the one cited by SmithKline Beecham could be used to support Havrix when there was data from four comparative studies described above.

The second reference cited by SmithKline Beecham compared the use of a 1" (25mm) needle to a 5/8" (16mm) needle for the injection of DTP-polio in children of 18 months of age. Aventis Pasteur MSD stated that it was difficult to see the relevance of this data to the current case. The study compared intramuscular injection using a 16mm, 25 gauge needle in the arm to the same needle in the anterolateral thigh to injection into the anterolateral thigh with a 25mm 25 gauge needle in infants of 18 months of age. Neither the vaccine, nor the site of injection nor the age of the vaccine recipients appeared to be relevant to this case. Where needle lengths were compared it was in the anterolateral thigh and with needles of different lengths but the same gauge. It was also important to stress that the generally held opinion was that infants of 18 months were unable to give a reliable account of local pain and its relevance to an injection.

Finally, the letter of complaint stated that the 25 gauge needle was not the recommended choice for adult administration of the intramuscular vaccines. In fact the recommendation was confusing. The Department of Health guidelines included a pictorial recommendation of intramuscular injection with a 25 gauge needle but written recommendation of intramuscular injection with a 23 gauge needle. Clearly the primary guide to the use of a product should be its SPC and the conclusion that could be drawn from the Department of Health guidelines and the SPC was that either a 23 or 25 gauge needle could be used for intramuscular injection.

Aventis Pasteur MSD submitted that with regard to the alleged breach of Clause 2, the authority of the author and the wide dissemination of the information were necessitated by the activity of SmithKline Beecham and its sales representatives. Despite the letters, personal discussion and the provision of the standard letter described above, SmithKline Beecham was unwilling to review its use of the 'fat-pad arm model'. Because of the gravity of the case being built against Avaxim and the time spent in discussion with SmithKline Beecham it was necessary to adopt a rapid and decisive response. Aventis Pasteur MSD was therefore left with no alternative but to exercise its obligation to reassure its customers through the letter. It was the use of models such as this that were likely to bring the industry into disrepute and not its willingness to provide reassurance to healthcare professionals.

PANEL RULING

The Panel noted that the Avaxim SPC stated it was available as a prefilled syringe containing one dose (0.5ml); it was indicated for active immunisation against infection caused by hepatitis A virus in susceptible adults and adolescents. Section 4.2 of the SPC headed Posology and Method of Administration stated that as Avaxim was absorbed the vaccine must be injected by the intramuscular route in order to minimise local reactions. Avaxim should be administered by intramuscular injections in the deltoid region. Avaxim must not be administered intradermally or intravenously. In exceptional circumstances (eg in patients with thrombocytopenia or in patients at risk of haemorrhage) the vaccine might be injected by the subcutaneous route. The SPC stated that protection did not occur immediately but over 90% of individuals would have protective levels of antibodies after 2 weeks.

The Havrix Monodose SPC stated that it was available as a prefilled glass syringe containing 1ml dose. It was indicated for active immunisation against infections caused by hepatitis A virus. It should be injected intramuscularly in the deltoid region. The Panel noted that the SPC provided by SmithKline Beecham did not include any reference to specific humoral antibodies against HAV being detected in more than 88% of vaccinees on day 15 although this was the impression given in SmithKline Beecham's response. The SPC did state that Havrix conferred protection against hepatitis A within 2-4 weeks.

The Panel noted Aventis Pasteur MSD's submission that its concern had arisen as a result of the number of enquiries it had received. The Panel also noted a standard letter sent out by the company's medical information department in response to individual enquiries it received further to an article on needle length by Poland *et al* (1997) in JAMA.

The Panel noted that in response to a letter from Aventis Pasteur MSD about the use of the arm model SmithKline Beecham had stated that it was 'a perfectly legitimate activity to discuss the issue of needle length in relation to adult and paediatric vaccination but this will be done to stress the importance for SmithKline Beecham's products as opposed to any of yours'. The letter from the practice nurse stated that at a study day she was 'told and shown on a model of the skin that the small needle attached to ('some') prefilled vaccines are not reaching the deltoid muscle, thus compromising seroconversion'. The nurse requested reassurance regarding needle length. Given the enquiries the company had received about needle length the Panel considered that it was reasonable for Aventis Pasteur MSD to distribute a 'Dear Healthcare Professional' letter to address the matter.

The letter at issue stated that the anxiety about needle length 'had been prompted by an arm model demonstration by another vaccine company.' SmithKline Beecham was not mentioned by name however the comparative data which followed on local reactions and seroconversion rates did state that the comparator was the SmithKline Beecham product ie Havrix. The Panel noted that SmithKline Beecham accepted that it had used the fat arm model and considered that this had led health professionals to contact Aventis Pasteur MSD about the needle length of Avaxim. In these circumstances the Panel did not consider that the reference in the letter in question to an arm model demonstration by another vaccine company was disparaging to SmithKline Beecham as alleged. No breach of Clause 8.1 was ruled.

The Panel then considered the data on local adverse reactions and seroconversion rates which were referenced to Zuckerman *et al* (1997). This was an open-label study which compared the seroconversion rates in HAV-seronegative healthy adult volunteers. A RIA method was modified to increase the sensitivity of the assay. At two weeks after the first dose the seroconversion rates were 95.7% (Avaxim) and 87.1% (Havrix) ($p<0.01$); at 8 weeks 100% (Avaxim) and 97.6% (Havrix). The study stated that both vaccines had a good safety profile with slightly better local reactogenicity results observed for Avaxim. The number and percentage of immediate reactions, local reactions and systemic reactions were compared in a table. The only statistically significant difference was in relation to local reactions which occurred less often in seronegative Avaxim vaccinees compared to Havrix vaccinees ($p<0.01$). The numerical differences for all reactions were in favour of Avaxim with the exception of immediate reactions in seropositive vaccinees where nobody in either group experienced such a reaction after first dose. The discussion acknowledged that the clinical protection conferred by either vaccine was likely to be similar. Seroconversion rates at week 2 showed that the immune response occurred more rapidly with Avaxim than with Havrix and that the establishment of clinical protection might be swifter. The study concluded that the data demonstrated the superior safety and immunogenicity profiles of Avaxim.

The Panel noted that the second Zuckerman *et al* study (1998) examined whether either Havrix or Avaxim could be given as a booster dose after Havrix had been administered as the primary dose and was thus not directly relevant. The reactogenicity of the two vaccines was similar except that 8% of subjects reported pain at the injection site following a booster dose of Havrix compared with none following Avaxim ($p=0.01$). With the exception of local pain both preparations were equally well tolerated.

No data had been submitted to show that one type of assay method (ELISA or RIA) benefited one vaccine over another.

The Panel examined the studies cited by SmithKline Beecham and noted that Ipp *et al* (1980) was in a paediatric population and Victor *et al* (1994) was a non-comparative study. Victor showed that after 14 days 96% of vaccinees had positive anti-HAV titres and after 30 days all vaccinees had seroconverted.

On balance the Panel considered the data in the letter concerning seroconversion was not misleading and ruled no breach of Clause 7.2 of the Code. The Panel was concerned that the letter did not fairly reflect the situation regarding local adverse reactions. The data was more limited than the impression given by the table and text of the letter. On balance the Panel decided that the letter was misleading in this regard and a breach of Clause 7.2 of the Code was ruled.

The Panel then considered the choice of needle. The Panel noted that the HMSO booklet 'Department of Health 1996 Immunisation against infectious disease' stated in the text at Section 5.5 that in administration for deep subcutaneous or intramuscular immunisation in adults a 23 gauge needle was recommended. There was some confusion as the illustration at the beginning of Section 5 clearly labelled the needles used for subcutaneous and intramuscular injections as 25 gauge.

The Panel noted that Avaxim used a 25 gauge needle which was attached to the syringe and could not be changed. The vaccine, syringe and needle were licensed as a complete entity. Thus querying the needle size in effect queried the basis for the licence. It was thus acceptable for the letter to refer to the 25 gauge needle used for Avaxim. No breach of Clause 7.2 was ruled.

The Panel then considered the data presented on the immunogenicity obtained with Avaxim using three different routes of administration; intramuscular, jet and subcutaneously. The data had probably been included to answer the concerns raised by SmithKline Beecham and to reassure healthcare professionals that seroconversion occurred even if Avaxim 'missed' the muscle. The data was from Fisch *et al* (1996) which had been carried out on healthy volunteers. The phrase 'It is important to stress that Avaxim is only licensed to be given intramuscularly' introduced the relevant section. The Panel noted the wording of the Avaxim SPC. In particular the need to inject via the intramuscular route in order to minimise local reactions and the reference to use of the subcutaneous route in exceptional circumstances. The Panel considered that the letter was misleading and a breach of Clause 7.2 was ruled.

The Panel did not consider that the letter brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

Complaint received **10 April 2000**

Case completed **28 June 2000**

CASE AUTH/1014/4/00

CONSULTANT ANAESTHETIST v ELAN PHARMA

Video shown by a representative

A consultant anaesthetist complained about a meeting he had attended where a representative from Elan Pharma had given a presentation followed by a video. The presentation was on Dopacard (dopexamine). The video was on pre-operative optimisation. The complainant stated that the video specifically avoided naming the medicine involved but it was impossible not to realise that it was dopexamine. The complainant alleged that the evidence for pre-operative optimisation was grossly overstated and unbalanced. Pre-operative optimisation was not a licensed indication for dopexamine. Elan's promotion of dopexamine for this indication was clearly a breach of the Code.

The Panel noted that Dopacard was a catecholamine indicated for short-term intravenous administration to patients in whom afterload reduction (through peripheral vasodilatation and/or renal and mesenteric vasodilatation), combined with a mild positive inotropic effect, was required for the treatment of exacerbations of chronic heart failure or heart failure associated with cardiac surgery. The Panel noted that the product was not licensed for pre-operative optimisation.

The meeting had started with a promotional presentation on Dopacard by the representative which was followed by the video which was entitled 'Optimisation: reducing mortality and morbidity in high-risk surgery'. The video introduced the concept of pre-operative optimisation and discussed a clinical paper which demonstrated positive results in terms of mortality and morbidity in high risk surgical patients who received peri-operative optimisation. Although not stated on the video, dopexamine was used in those patients randomised to the protocol group. The video reviewed a second clinical paper where patients received pre-operative optimisation with either adrenaline or dopexamine. Again dopexamine was not referred to in the video but viewers were told that two different catecholamines were used. It was stated that there was a dramatic fall in mortality in the optimised groups compared with control.

The Panel noted that Elan had stated that its representative introduced the video as being educational and non promotional and not linked to dopexamine and that she had clearly said in response to a question that dopexamine was not licensed for pre-operative optimisation and could not be recommended. The Panel considered that the video had some educational content. It was however linked to dopexamine. It could not be considered to be non-promotional. Data was presented from two clinical studies which had involved the use of dopexamine. The Panel noted the submission from Elan that the literature included studies in which successful optimisation had been conducted with dobutamine, adrenaline and intravenous fluids alone. Only clinical studies involving dopexmine were referred to in the video. The Panel considered that an audience with specialist knowledge would make the connection between the data presented in the video and dopexamine, particularly as the video had been shown immediately after a presentation on dopexamine. The Panel considered that the video promoted Dopacard for an unlicensed indication. A breach of the Code was ruled. The Panel considered that there was a considerable weight of evidence to support the benefit of pre-operative optimisation. However the video only referred to clinical studies involving the use of dopexamine. In this regard the video was unbalanced. A further breach of the Code was ruled.

COMPLAINT

A consultant anaesthetist complained about a meeting he had attended where a representative from Elan Pharma Limited had given a presentation followed by a video. The representative had given a presentation on Dopacard (dopexamine). The video was on pre-operative optimisation.

The complainant stated that the video specifically avoided naming the medicine involved but it was impossible not to realise that it was dopexamine. This was not only by the fact that it followed on from a presentation on dopexamine, but because the constant reference to vasodilatation made the identity of the medicine obvious to everybody in the audience.

The complainant alleged that the evidence for pre-operative optimisation was grossly overstated and unbalanced. Pre-operative optimisation was not a licensed indication for dopexamine. Elan's promotion of dopexamine for this indication was clearly a breach of the Code.

RESPONSE

Elan Pharma submitted that the meeting in question was one of a regular series of educational meetings organised by the specialist registrars in anaesthetics at a children's hospital. The specialist registrar organising this particular meeting approached Elan's local representative and requested she make available an educational video produced by Elan on the optimisation of high risk surgical patients. The representative was also invited to make a short promotional presentation on dopexamine at the start of the meeting, separate from the educational part of the meeting.

Elan stated that the meeting was attended by 13 specialist registrars and two people from the British Medical Association. The representative began by stating clearly the licensed indications for dopexamine (short-term intravenous administration to patients in whom afterload reduction (through peripheral vasodilatation, and/or renal and mesenteric vasodilatation), combined with a mild positive inotropic effect was required for the treatment of exacerbations of chronic heart failure, or heart failure associated with cardiac surgery) and proceeded to show the slides describing the pharmacological profile of the medicine. The video was introduced by the representative with a clear statement that it was not

linked to dopexamine. The representative also stated clearly that the contents were educational and not promotional, and the specific product therapy would not be discussed. In response to a direct question regarding the use of dopexamine in optimisation, the representative stated clearly that the medicine did not have a licence for this indication and could not be recommended.

Elan stated that it was a relatively new company in the field of critical care and it had produced an educational video on an area of considerable current interest to anaesthetists and intensivists. Optimisation of high risk surgical patients was also a subject of some controversy in this area, principally concerning the resource implications. The company submitted that it was, therefore, an appropriate subject to cover in this educational video in which respected opinion leaders discussed the physiological goals as well as the practical aspects of implementation. The process involved the optimisation of tissue oxygen delivery, usually towards a predetermined level, in patients undergoing major surgery who were at risk of post-operative complications due to concomitant illness or diminished functional reserve in major organ systems. A package of interventions was employed which involved oxygen, intravenous fluids, blood products and vasoactive medicines. The literature contained a wealth of data on the significant benefits of this intervention in terms of post-operative morbidity and mortality.

The video made no reference to medicines used as part of the optimisation package and, therefore, made no promotional claims. One of the participants in the video stated that the medicine used should be one which improved blood flow (not vasodilatation as claimed by the complainant). This was, after all, a key objective of the process. Flow could be improved by administering medicines which dilated vascular beds or increased cardiac output. There were several products which shared these properties and so the video did not make specific implicit reference to dopexaine. Indeed the literature included studies in which successful optimisation had been conducted with dobutamine, adrenaline, and, indeed, intravenous fluids alone. Elan did not believe that the video promoted the use of dopexamine in this indication.

Elan submitted that the weight of evidence supporting the concept of optimisation was considerable. A literature search using Medline, EmBase and BIOSIS revealed no studies in which optimisation did not result in improved outcome. It believed the video to be a fair representation of the balance of evidence, therefore, and refuted strongly the complainant's view that the evidence was overstated and unbalanced.

In summary, Elan believed that its representative conducted herself in accordance with the spirit and the letter of the Code. An educational, non-promotional video on a topic of clinical relevance was presented which reflected the balance of evidence in the published literature. It did not accept that any clauses of the Code had been breached.

PANEL RULING

The Panel noted that Dopacard was a catecholamine indicated for short-term intravenous administration to patients in whom afterload reduction (through peripheral vasodilatation and/or renal and mesenteric vasodilatation), combined with a mild positive inotropic effect, was required for the treatment of exacerbations of chronic heart failure or heart failure associated with cardiac surgery. The Panel noted that the product was not licensed for pre-operative optimisation.

The Panel noted that the meeting at which the video had been shown started with a promotional presentation on Dopacard by the representative. This was followed by the video which was entitled 'Optimisation: reducing mortality and morbidity in high-risk surgery'. The video introduced the concept of pre-operative optimisation and discussed a clinical paper by Boyd *et al* 1993 which demonstrated positive results in terms of mortality and morbidity in high risk surgical patients who received peri-operative optimisation. Although not stated on the video dopexamine was used in those patients randomised to the protocol group. Subsequent favourable pharmacoeconomic analyses of these results (Bennett 1995 and Guest *et al* 1997) were also discussed. The video reviewed a second clinical paper (Wilson *et al* 1999) where patients received pre-operative optimisation with either adrenaline or dopexamine. Again dopexamine was not referred to in the video but viewers were told that two different catecholamines were used. It was stated that there was a dramatic fall in mortality in the optimised groups compared with control. Viewers were also told that the study also demonstrated significant differences in the levels of post-operative morbidity between the two treatment groups, suggesting that the choice of catecholamine might be important. Having presented the clinical results the video went on to discuss the techniques of pre-operative optimisation and patient selection. Finally the video examined the role of medicines. It was stated by one consultant anaesthetist that where administration of fluids alone was not sufficient he used an agent which increased cardiac output and also increased flow to various organ systems of the body.

The Panel noted that Elan had stated that the representative introduced the video as being educational and non promotional and not linked to dopexamine and that she had clearly said in response to a question that dopexamine was not licensed for pre-operative optimisation and could not be recommended.

The Panel considered that the video had some educational content. It was however linked to dopexamine. The video could not be considered to be non-promotional. Data was presented from two clinical studies which had involved the use of dopexamine. The Panel noted the submission from Elan that the literature included studies in which successful optimisation had been conducted with dobutamine, adrenaline and intravenous fluids alone. Only clinical studies involving dopexmine were referred to in the video.

The Panel considered that an audience with specialist knowledge would make the connection between the data presented in the video and dopexamine, particularly as the video had been shown immediately after a presentation on dopexamine.

The Panel considered that the video promoted Dopacard for an unlicensed indication. A breach of Clause 3.2 of the Code was ruled.

The Panel considered that there was a considerable weight of evidence to support the benefit of pre-operative optimisation. This was summarised in a review article by Boyd. However the video only referred to clinical studies involving the use of dopexamine. The video did not discuss any clinical studies in which dopexamine had not been used. In this regard the video was unbalanced. A breach of Clause 7.2 of the Code was ruled.

Complaint received **13 April 2000**

Case completed **12 July 2000**

CASE AUTH/1016/4/00 *NO BREACH OF THE CODE*

PHARMACIST v JANSSEN-CILAG

Presentation on Risperdal

A pharmacist complained about a presentation on Risperdal (risperidone) given by a Janssen-Cilag representative. The representative had clearly advocated its use for acute agitation/confusion in the elderly 'in anyone currently on thioridazine without the side-effects of daytime sedation and extrapyramidal symptoms', recommending a low dose such as 0.5mg at night. It was alleged that the information given at the meeting was inconsistent with Risperdal's summary of product characteristics. Two of the doctors present at the meeting had said that they had not been aware that Risperdal was not licensed for the indication discussed at the meeting. The response from Janssen-Cilag was sent to the complainant for his further comment.

The Panel noted that Risperdal was indicated for the treatment of acute and chronic schizophrenic psychoses and other psychotic conditions in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility and suspiciousness) and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) were prominent. Risperdal also alleviated affective symptoms (such as depression, guilt feelings and anxiety) associated with schizophrenia. For the elderly a starting dose of 0.5mg bd was recommended which could be adjusted with 0.5mg bd increments to 1 to 2mg bd. The detail aid used by the representative at the meeting concentrated on the use of Risperdal in the elderly. The detail aid stated that Risperdal should be considered a first choice treatment in elderly patients because of its highly significant reduction of symptoms such as hostility/aggressiveness, excitement, suspiciousness, etc, leading to an improvement in agitation, antisocial behaviour and daily routine. The sales presentation featured similar material. The Panel was concerned that neither the detail aid nor the sales presentation included a clear statement of Risperdal's licensed indications in the main body of the text.

The Panel noted that the complainant had not attended the meeting but had overheard it from an adjoining room. He had not had the benefit of the visual aids. The Panel noted the complainant's submission regarding the impression gained about Risperdal's licensed indication and dosage by two of the practice partners present. The Panel considered that it was difficult to determine precisely what had been said about Risperdal's licensed indication and dosage at the meeting. The Panel noted Janssen-Cilag's submission regarding the difficulty in responding further given that it was unaware of the identity of the specific practice. The representative would be involved in numerous such discussions each week and hence he could only surmise what he might have said from his general experience and usual practice. It was impossible in such circumstances to determine where the truth lay. The parties' accounts differed. On balance the Panel ruled no breach of the Code.

A pharmacist complained about a presentation about Risperdal (risperidone) given by a representative from Janssen-Cilag Ltd.

COMPLAINT

The complainant stated that whilst working in an adjacent room in a practice, he was able to hear a presentation on Risperdal. The representative giving the presentation clearly advocated the use of Risperdal for acute agitation/confusion in the elderly 'in anyone currently on thioridazine without the side-effects of daytime sedation and extrapyramidal symptoms'. The representative recommended a low dose such as 0.5mg at night.

The complainant noted that the summary of product characteristics (SPC) for thioridazine made specific reference to agitation and restlessness in the elderly, unlike the SPC for Risperdal which quoted the following indications and doses:

> *'Therapeutic indications:* Risperdal is indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of

speech) are prominent. Risperdal also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Elderly: A starting dose of 0.5mg bd is recommended. This dosage can be individually adjusted with 0.5mg bd increments to 1 to 2mg bd.'

The complainant considered that the information given at the meeting did not conform to the Risperdal SPC in breach of Clause 3.2 of the Code.

The complainant stated that following the meeting he had discussed the issue with two of the partners present, who were unaware that Risperdal was not licensed for the indication discussed in the presentation. The complainant stated that he was aware that Risperdal was being used for this unlicensed indication in secondary care and general practitioners might be asked to take over the clinical responsibility for prescribing the product. However, he was concerned that general practitioners might be encouraged to prescribe products without being aware that the indication was unlicensed and therefore they assumed full responsibility for the product unknowingly.

RESPONSE

Janssen-Cilag noted that the complaint was that the representative in question had advocated the use of Risperdal in acute confusion in the elderly 'in anyone currently on thioridazine'.

After discussion with the representative, the company was certain that no breach of the Code had occurred, as the representative was aware of the issues surrounding this area of the licensed indications.

Furthermore, Janssen-Cilag considered that the complaint described an unlikely statement: any medical practitioner would be aware that acute confusion was by its very nature of short duration, and that the objective of management was to discover and treat the underlying cause. Therefore, patients would be unlikely to remain on neuroleptic medication for more than a few days. To use the phrase 'anyone currently on…' suggested ongoing or continuing prescription (of an antipsychotic or sedative in this case) and referred to a chronic condition, where agitation or restlessness were the result of psychotic illness, being treated. Janssen-Cilag stated that it would like to make it clear that the concept under discussion was in fact a set of symptoms within licence, not 'acute confusion'.

Janssen-Cilag explained that psychotic conditions, especially in elderly people, could manifest as agitation and restlessness. This was emphasised in the detail aid which the representative was working through with those in attendance. He did not give an audio visual presentation or use slides.

Janssen-Cilag had spoken to the representative in question, who had a clear understanding of the licensed indications and which conditions Risperdal was not licensed for. The training course which the representative underwent included a session on the differential diagnosis of mental disorder in the elderly, and there was a session on the product characteristics of Risperdal, in which the issues of which conditions were in and were not in licence were discussed. The representative was advocating the use of Risperdal in place of older neuroleptics in elderly patients with psychotic conditions.

Janssen-Cilag stated that the representative said that he might have replied to a question about dosage, and was reflecting the opinions of local specialists in response to a question, and that he stated the 0.5mg bd was, in the opinion of many consultant psychiatrists in the psychiatry of old age, an appropriate starting dose in elderly patients as sensitivity to antipsychotic drugs might be enhanced in this group.

In summary Janssen-Cilag stated that its enquires and examination of materials pointed to the representative being clearly trained on the subject which formed the core of this claim and it was clear that the symptoms mentioned were part of the wider picture of psychosis and it was just these symptoms which general practitioners were called upon to treat in their patients. Discussion of the topic would therefore be appropriate.

Following a request for further information Janssen-Cilag noted that it was very difficult for the representative to recall the specific meeting referred to or what exactly was said. The representative would be involved in numerous such discussions each week and hence he could only surmise what he might have said from his general experience and usual practice using the sales aid or sales presentation.

Janssen-Cilag stated that the representative was fully aware of the starting dose stated in the SPC and this was reflected in the sales materials used. The representative had stated that he was often asked what the local consultant's practice was when initiating Risperdal. In answer to this specific question he would reflect the practice of the local psychogeriatrician, which in many cases would be a starting dose of 0.5mg at night. This however would be as a legitimate reply to the specific question posed and he would discuss this in the context of the dosing recommendation on the SPC.

Janssen-Cilag noted that the SPC stated that the recommended starting dose was 0.5mg bd which did not preclude the first dose being given at night, ie 0.5mg at night, and continuing in a bd manner from the following morning. Indeed it was clinically sound to do this so that established side effects such as sedation or dizziness if they occurred would be experienced at night when the patient would normally be in bed.

Janssen-Cilag stated that either of these scenarios could explain the alleged events regarding dosing advice but without knowing the identity of the specific practice it was unable to comment further.

Janssen-Cilag noted that although the SPC recommended a starting dose of 0.5mg bd for the elderly it did not preclude the use of a lower starting dose. It was generally accepted in clinical practice that some patients required a lower starting dose or longer titration period and this was relevant to the

general dosing of Risperdal. It was a measure adopted by clinicians solely to enhance safety in potentially sensitive patients and with the objective of keeping the administered dose to the lowest conferring efficacy.

Janssen-Cilag was concerned that as the complainant was not in the same room as the representative he would have been unaware of any explanatory visual aids being used by the representative. Also if he was concentrating on another activity in the adjacent room he might not have heard all of the discussions, or may have taken what was heard out of context.

Janssen-Cilag provided copies of the relevant detail aid and also of the sales presentation both of which the company submitted clearly presented symptoms such as agitation in the context of an underlying psychosis and clearly stated the recommended starting dose of 0.5mg bd. The company explained that representatives received briefings on the use of such materials and the positioning and dosing of Risperdal at comprehensive training programmes during which the SPC was discussed in detail during a 90-minute session conducted by the product manager. Each delegate was provided with a copy of the SPC and was walked through it virtually line by line. The product manager ensured that the indications for Risperdal and the dosing in the elderly were clearly understood during this session. Janssen-Cilag provided an agenda for the training programme as well as a representative's learning diary accompanying the training programme.

Janssen-Cilag reiterated that, from the evidence presented, it did not believe that its representative had acted improperly. The company therefore did not accept that there had been a breach of Clause 3.2 of the Code.

The response from Janssen-Cilag was sent to the complainant for further comment.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant reiterated that he considered that Risperdal was being promoted for 'cognitive impairment in the elderly'. He provided a recent review pertaining to this (Falsetti 2000) which although published in the United States, was clearly discussing an unlicensed indication. The review concluded that more clinical trials were needed to elucidate risperidone's role in controlling agitation in patients with dementia. The complainant considered that there was a fine line between the licensed indications of risperidone, which might be included under the 'other psychotic conditions', and its role in treating agitation and restlessness in elderly patients with dementia. The complainant stated that given that 70% of patients in nursing homes had dementia and that 90% of these exhibited aggressive or agitated behaviour it was likely that they would be receiving some form of neuroleptic medication. If this were thioridazine, as was common, then would changing them to risperidone be outside of the product licence?

The complainant agreed that the initial dosage of 0.5mg at night was sensible. However, continuing with bd dosing the following morning was not mentioned. This also would not concur with the representative's statement about 'avoiding daytime sedation'.

The complainant stated that the fact that he was not in the same room as the representative was bound to be an issue. However, being a pharmacist, one was always tuned in to conversations regarding use of medicines and the complainant did not consider that the comments heard were taken out of context. This was confirmed following a discussion with two of the partners following the meeting.

PANEL RULING

The Panel noted that the Risperdal SPC stated that it was indicated for the treatment of acute and chronic schizophrenic psychoses and other psychotic conditions in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility and suspiciousness) and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) were prominent. Risperdal also alleviated affective symptoms (such as depression, guilt feelings and anxiety) associated with schizophrenia. For the elderly a starting dose of 0.5mg bd was recommended. This dosage could be adjusted with 0.5mg bd increments to 1 to 2mg bd.

The SPC for thioridazine (ref: ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999/2000) stated that it was indicated for schizophrenia, treatment of symptoms and prevention of relapse; mania and hypomania; as an adjunct to the short-term management of anxiety, moderate to severe psychomotor agitation, excitement, violent or dangerously impulsive behaviour; agitation and restlessness in the elderly. The Panel noted that thioridazine had broader indications than Risperdal; the symptom complex for psychotic patients to be treated with Risperdal had to be associated with positive and/or negative symptoms.

The Panel noted that the detail aid was entitled 'Just because they're old doesn't mean they should be given old drugs' and concentrated on the use of Risperdal in the elderly. Patient profiles were given on the first few pages of the detail aid illustrating, in particular, positive symptoms such as thought disturbance. Subsequent pages detailing the efficacy, side effects and dosage of Risperdal, and the summary page, all carried the strap-line 'from psychotic to cool calm and collected'. A page detailing side-effects stated that Risperdal treatment was associated with a low level of sedation and referred to sedation as a side-effect in 'the agitated patient'. The detail aid concluded by stating that Risperdal should be considered a first choice treatment in elderly patients because of its highly significant reduction of symptoms such as hostility/aggressiveness, excitement, suspiciousness, etc, leading to an improvement in agitation, antisocial behaviour and daily routine. The sales presentation featured similar material. The Panel was concerned that neither the detail aid nor the sales presentation included a clear statement of Risperdal's licensed indications in the main body of the text.

The Panel noted the recommended starting dose of 0.5mg in the elderly. The Panel noted that the section of the detail aid headed 'Dosage' stated that 'The starting dose is 0.5mg bd'. The Panel did not accept Janssen-Cilag's submission that the recommended starting dose did not preclude the use of a lower starting dose; the Panel considered that promoting a lower starting dose would be inconsistent with the SPC.

The Panel noted that the complainant had not attended the meeting in question but had overheard it from an adjoining room. He had not had the benefit of the visual aids. The Panel noted the complainant's submission regarding the impression gained about Risperdal's licensed indication and dosage by two of the practice partners present.

The Panel considered that it was difficult to determine precisely what was said about Risperdal's licensed indication and dosage at the meeting. The Panel noted Janssen-Cilag's submission regarding the difficulty in responding further given that it was unaware of the identity of the specific practice. The representative would be involved in numerous such discussions each week and hence he could only surmise what he might have said from his general experience and usual practice.

The Panel noted that it was impossible in such circumstances to determine where the truth lay; the parties' accounts differed. On balance the Panel ruled no breach of Clause 3.2 of the Code.

Complaint received **18 April 2000**

Case completed **18 July 2000**

CASE AUTH/1018/4/00

INSULIN DEPENDENT DIABETES TRUST v NOVO NORDISK

Mailing about NovoPen 3

The Insulin Dependent Diabetes Trust complained about a mailing sent to one of its members by Novo Nordisk. The mailing consisted of a letter and a leaflet about NovoPen 3, an insulin injection device. There were two issues of concern. Firstly that Novo Nordisk had acquired the member's name and address. How did it know that he had diabetes, especially as he did not use the insulin for which the pen was suitable? Secondly, the member knew that pharmaceutical companies were allowed to advertise devices to patients and that they were not allowed to advertise medicines. NovoPen 3 was designed such that it could only be used with Novo Nordisk human insulins and it therefore appeared that the mailing was indirectly advertising a specific brand and species of insulin to a patient.

The Panel noted that the Code applied to the promotion of medicines and not to the promotion of devices *per se*. In the Panel's view, if a device could only be used with a specific medicine, or if no other manufacturer's medicine could be used with the device, then promotion of that device would constitute promotion of the medicine and the matter would be covered by the Code. The Panel noted that no other manufacturer's insulin cartridges could be used in the NovoPen system. Promotion of the NovoPen 3 system therefore constituted promotion of Novo Nordisk insulin cartridges and was thus within the scope of the Code.

The Panel did not accept the submission that the aim of the mailing was to make people on Novo Nordisk insulin vials aware that an alternative method of delivery was now available. The mailing had been distributed to a broad audience comprised of those who had indicated in a consumer survey that somebody in their household had diabetes. The person responding to the survey was not necessarily the person with diabetes. The Panel noted from the survey form provided that there was no differentiation between insulin dependent diabetes and non-insulin dependent diabetes and nor were respondents asked to state which brand of insulin (if any) was used.

The Panel noted that the mailing made favourable claims for the NovoPen 3 system. The leaflet described insulin administration using a syringe and vial as awkward and embarrassing. If they wanted further information on NovoPen 3 recipients of the mailing could request a patient video.

The Panel considered that the mailing and video constituted an advertisement to the public for a prescription-only medicine. The mailing and video would encourage patients to ask their doctors to prescribe the NovoPen 3 device and in effect a Novo Nordisk insulin cartridge. Breaches of the Code were ruled.

In relation to the question of the confidentiality of the identity of the recipient of the mailing, the Panel noted Novo Nordisk's response that the names and addresses of the intended recipients were not known to the company. The Panel was aware that mailing lists of those suffering from various conditions were available and that these were derived from consumer product surveys. The Panel ruled that there had been no breach of the Code in that regard.

Upon appeal by Novo Nordisk, the Appeal Board accepted that patients were demanding more

information about medicines and that pharmaceutical companies should respond appropriately within the requirements of the Code, in particular Clause 20. The Appeal Board noted that the Code did not cover the promotion of devices *per se*.

The Appeal Board accepted the merits of pen delivery systems and the need to increase awareness of them but that was not the issue.

The Appeal Board noted that bearing in mind European law (in particular the prohibition in the European Directive on the Advertising of Medicinal Products for Human Use) the sole issue for it to determine was whether promotion of NovoPen 3 constituted promotion of prescription only medicines directly to the public contrary to the provisions of Clauses 20.1 and 20.2 of the Code.

The Appeal Board noted that insulin was a prescription only medicine. The NovoPen 3 could only be used with one of eight licensed insulin medicines marketed by Novo Nordisk. It could not be used with insulin marketed by any other manufacturer. This was not unusual.

The Appeal Board noted that the mailing had been distributed to a broad audience comprised of those who had indicated in a consumer survey that somebody in their household had diabetes.

The Appeal Board considered that if a device could only be used with a specific medicine, or if no other manufacturer's medicine could be used with the device, then promotion of that device would constitute promotion of the medicine and the matter would be covered by the Code. The Appeal Board considered that the mailing and video by referring to the NovoPen 3 constituted promotion of Novo Nordisk's eight insulin medicines to the general public. The materials would direct members of the public towards specific medicines produced by Novo Nordisk and would thus encourage members of the public to ask their doctors to prescribe the NovoPen 3 device and in effect a Novo Nordisk insulin cartridge. The Appeal Board upheld the Panel's rulings of breaches of the Code. The appeal was thus unsuccessful.

The Insulin Dependent Diabetes Trust complained about a mailing which one of its members had received from Novo Nordisk Pharmaceuticals Ltd and which concerned the NovoPen 3, an insulin injection device. The mailing consisted of a letter and a leaflet. The letter was headed 'Information for people using insulin' and stated, *inter alia*, 'The NovoPen 3 system has been designed to make life with injections as easy and simple as possible – it is a portable, convenient and very discreet way to take insulin that can help you become more independent and in control of your diabetes'. Recipients were informed that if they were interested in receiving further information on NovoPen 3 they could return an enclosed reply card or contact the NovoPen 3 Helpline; they would receive a video which demonstrated the device and included interviews with patients and their specialist nurses. The accompanying leaflet was headed 'NovoPen 3. The discreet, convenient insulin delivery system you can take anywhere.' The leaflet described injections with NovoPen 3 as 'virtually pain free'.

COMPLAINT

The complainant stated that there were two issues which concerned its member.

1 Confidentiality – how did Novo Nordisk acquire his name and address in order to send him the letter and how did it know that he had diabetes, especially as he did not use the insulin for which this pen was suitable?

2 He realised that pharmaceutical companies were allowed to advertise medical devices to patients and that they were not allowed to advertise medicines. However, the NovoPen 3 was designed in such a way that it could only be used with Novo Nordisk human insulins and it therefore appeared that this advertising package was indirectly advertising a specific brand and species of insulin to him as a patient.

One had to assume by the very nature of advertising that the material he received from Novo Nordisk was trying to persuade him to use its pen and therefore its human insulins. It appeared that this was in breach of the regulation forbidding advertising medicines directly to patients and, if not actually in breach, it could be easily interpreted as circumventing the regulations in order to persuade him to ask his physician to prescribe that particular pen and therefore that particular brand and species of insulin.

RESPONSE

Novo Nordisk stated that approximately two weeks after Lord Hunt's announcement regarding the availability of certain insulin delivery devices and needle devices on NHS prescription, Novo Nordisk sent a mailing to 15,000 randomly selected households which had indicated in a consumer products survey that someone in their household had diabetes. The database was held by a company which specialised in consumer databases and all responders to the consumer products survey questionnaire had the option of allowing information about them to be passed to third parties. A copy of a 1998 survey form was provided. To the best of Novo Nordisk's knowledge and belief, no mailing was sent to anyone who had indicated an unwillingness to receive communication from third parties. The names and addresses of the intended recipients were not known to Novo Nordisk.

The insulin cartridges used in NovoPen 3 were 3ml insulin cartridges manufactured by Novo Nordisk. There was a wide range of Novo Nordisk insulins available in 3ml insulin cartridges. No other manufacturers' insulin cartridges could be used in this pen system.

Novo Nordisk strongly refuted the allegation made in the complainant's letter that it was trying to persuade any patient to change their insulin from their current species or brand to Novo Nordisk's human insulin. The NovoPen 3 was a device and, as such, Novo Nordisk was allowed to advertise it to the general public. Novo Nordisk fully understood and respected the law in this area, which did not allow the promotion of an individual prescription only medicine direct to the public. Novo Nordisk had not mentioned the names of its branded insulins and had

even removed the name from the picture of the cartridge above the picture of the NovoPen 3 in case the mailing could be misconstrued. Novo Nordisk submitted therefore that it had taken considerable care not to advertise its insulins and not to make any claims for its insulins but had simply concentrated on the device.

The NovoPen 3 Helpline referred to was an externally managed facility set up to handle postal and telephone response to this mailing. Postal requests were sent an information pack containing a leaflet and video. A telephone number was available to enable enquirers to telephone to request the information pack or ask questions about NovoPen 3. Complex or non-NovoPen 3 related calls were transferred to Novo Nordisk's Customer Care Centre.

A transcript of the video was provided. Only the questions were scripted because real patients were used and Novo Nordisk had no control over their answers.

Novo Nordisk's aim with this mailing, in the light of the Government's announcement regarding reimbursement of devices and needles, was to make people on Novo Nordisk insulin vials aware that an alternative method of delivery was now available because it knew that many people in the past had avoided pen delivery systems owing to the cost of needles. Novo Nordisk agreed with the Q and A from the ABPI's Informed Patient Initiative Task Force which stated that 'A better informed and managed patient with a chronic condition eg diabetes, is likely to stay clear of debilitating complications …'.

In summary therefore, Novo Nordisk firmly believed that it had not broken any rules of confidentiality and that it had not promoted any specific medicine to the public. It believed that it had tried to raise awareness of its device to people who might benefit from this knowledge, in view of the Government's willingness to acknowledge the benefits of insulin delivery devices as being more accurate and less painful than conventional syringes and needles.

PANEL RULING

The Panel noted that the Code applied to the promotion of medicines and not to the promotion of devices *per se*. In the Panel's view, if a device could only be used with a specific medicine, or if no other manufacturer's medicine could be used with the device, then promotion of that device would constitute promotion of the medicine/s and the matter would be covered by the Code. The Panel noted that no other manufacturer's insulin cartridges could be used in the NovoPen system. Promotion of the NovoPen 3 system therefore constituted promotion of Novo Nordisk insulin cartridges and was thus within the scope of the Code.

The Panel noted that Clause 20.1 prohibited the advertising of prescription only medicines to the general public. Clause 20.2 of the Code permitted information to be supplied directly or indirectly to the general public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine.

The Panel did not accept the submission that the aim of the mailing was to make people on Novo Nordisk insulin vials aware that an alternative method of delivery was now available. The mailing had been distributed to a broad audience comprised of those who had indicated in a consumer survey that somebody in their household had diabetes. The person responding to the survey was not necessarily the person with diabetes. The Panel noted from the survey form provided that there was no differentiation between insulin dependent diabetes and non-insulin dependent diabetes and nor were respondents asked to state which brand of insulin (if any) was used.

The Panel noted that the letter and the accompanying leaflet made favourable claims for the NovoPen 3 system. The leaflet described insulin administration using a syringe and vial as awkward and embarrassing. If they wanted further information on NovoPen 3 recipients of the mailing could request a patient video. The Panel examined the transcript of the video. The patients featured on the video discussed their fears of having to use a syringe which they then compared to the use of a pen. One patient urged viewers to 'Give it a go and basically, you know, it will make a difference to you'. A voice-over stated that Novo Nordisk had developed the very first insulin pen; claims were made for the NovoPen 3. It was stated that Novo Nordisk were 'the only manufacturers to make everything you need for insulin injections: insulin, pens and needles – because that way we know you'll have a perfectly matched system'. At the end of the video the voice-over referred patients to the NovoPen 3 instruction manual (a copy of which was not before the Panel) for detailed information.

The Panel considered that the mailing and video constituted an advertisement to the public for a prescription only medicine and ruled a breach of Clause 20.1. The mailing and video would encourage patients to ask their doctors to prescribe the NovoPen 3 device and in effect a Novo Nordisk insulin cartridge. A breach of Clause 20.2 was also ruled. These rulings were appealed.

In relation to the question of the confidentiality of the identity of the recipient of the mailing, the Panel noted Novo Nordisk's response that the names and addresses of the intended recipients were not known to the company. The Panel was aware that mailing lists of those suffering from various conditions were available and that these were derived from consumer product surveys. The Panel considered the matter under the general requirements of Clause 9.1 and ruled that there had been no breach of the Code in that regard. This ruling was not appealed.

APPEAL BY NOVO NORDISK

Novo Nordisk stated that its strong belief was and is that it did not breach the Code with its recent mailing about NovoPen, one of its insulin delivery devices,

and wished to challenge the Panel's views on several issues.

Novo Nordisk stated that the Panel's view that promoting a device which could only be used with one manufacturer's insulins was directly promoting those insulins was surely an oversimplification. If a manufacturer had only one marketed product would promoting the name of that manufacturer constitute promoting that product? Probably, but this would presumably be allowable under the Code since the product would not be mentioned specifically. No mention of any of its insulins was made. It was also important to remember that a wide range of human insulins (soluble, isophane, pre-mixed biphasic and analogue) with different clinical uses could be administered in this device – 'insulin' was a generic term. Therefore it felt it did not advertise any specific medicinal product directly to the general public.

Novo Nordisk pointed out that in Europe there had been direct to consumer awareness campaigns for several years with devices (eg France and Germany) which had caused no concerns to the European authorities because a specific medicinal product was not mentioned. The advertising directive was the controlling legislation in this field and its overarching rationale and aim was that public health was enhanced by the provision of appropriate information about medicinal products and health. Consistent with this, patients must be protected from 'excessive and ill considered claims' about medicinal products. Factual information that related directly or indirectly to products was allowed provided it contained no claims concerning a specific medicinal product. It was implicit that manufacturers had a role in health education but, in relation to information supplied direct to the public, the law reflected the fact that care should be taken to avoid undermining the doctor/patient relationship. That relationship would be undermined by direct promotion of a specific prescription only medicine that encouraged a patient to have a preconceived notion of what product was needed to treat the patient's condition and consequently to ask the doctor for that specific medicinal product.

Novo Nordisk stated that it was against this rationale and these considerations that the individual provisions of the UK regulations and the Code, that reflected the law and good practice, must be interpreted. The law also recognised that restrictions on advertising, therefore, of freedom of speech, must be proportionate to the aim of the law in protecting public health. Novo Nordisk respectfully suggested that this consideration was particularly important in today's environment where a less paternalistic attitude to healthcare was seen as appropriate and patients' thirst for information about products was gradually being met through the provision of information in the form of detailed patient leaflets, European public assessment reports, access to the ABPI Compendium of Data Sheets and Summaries of Product Characteristics, and health education campaigns – all of which the ABPI had encouraged.

Novo Nordisk believed that it was against this background that one must consider whether information about a medical device (the advertising of which in principle was not forbidden) to deliver a range of medicines, but which did not focus on a specific medicinal product, should be judged. This was particularly so when the patient population at whom the information was directed – in this case people with diabetes – could reasonably be expected to have been advised by doctors on their need for insulin and what specific product was appropriate for each of them. Such patients would have a relatively sophisticated understanding of the medicines themselves but might not have the same knowledge about advances in technology in relation to the delivery of insulins and changes in the reimbursement system. Could it really sensibly be suggested that by alerting patients to the existence of alternative methods of delivering Novo Nordisk insulins the doctor/patient relationship would be undermined, and with it public health, in any way at all? Novo Nordisk made no reference to a specific medicinal product; no claims related to a specific medicinal product (it had even deleted the name of the particular product on the example of a cartridge in the picture on the mailing) and it had not sought to undermine the doctor/patient relationship in any way. On the contrary, it respectfully suggested that to stop manufacturers promoting the devices by which their products could be administered would be wholly disproportionate to the rationale of the legislation and the Code. Far from protecting patients, such an interpretation of the rules actually constituted a perpetuation of a paternalistic approach to informing patients that was neither required nor appropriate under the legislation and Code.

Novo Nordisk referred to advertisements for pen devices placed by other companies in material for the general public. Novo Nordisk did not propose to complain about these advertisements because it considered it was important that patients had as much information about insulin delivery devices as possible.

At the appeal hearing background information about diabetes, the change in reimbursement which meant that pen needles and reusable insulin pens became available on prescription and the arrangements for the consumer survey was given. Details were given of the eight insulins, all with separate licences, produced by Novo Nordisk in cartridges to fit the NovoPen 3.

At the appeal hearing it was explained that if a patient currently using syringes and needles asked their doctor for a pen, the prescriber would give the patient the cartridge and pen version of the insulin currently being used by the patient. It was highly unlikely that the prescriber would change the patient's insulin. At the appeal hearing the company provided a separate paper on the application of European law to this issue. The paper discussed in detail the European Directive on the advertising of medicinal products for human use as well as the European Convention on Human Rights. This was also mentioned in the company's submission at the appeal.

APPEAL BOARD RULING

The Appeal Board noted the company's submission regarding the relevant law including European law.

The Appeal Board's role was to make a decision regarding Clause 20 of the Code in the light of European law. The Appeal Board noted that statements relating to human health or diseases were excluded from the Code provided there was no reference, either direct or indirect, to specific medicines. The Appeal Board accepted that patients were demanding more information about medicines and that pharmaceutical companies should respond appropriately within the requirements of the Code, in particular Clause 20. The Appeal Board noted that the Code did not cover the promotion of devices *per se*. It noted the supplementary information to Clause 4.1 of the Code 'Advertisements for Devices' which stated that where an advertisement related to the merits of a device used for administering medicines, such as an inhaler, which was supplied containing a variety of medicines, the prescribing information for one only needed to be given if the advertisement made no reference to any particular medicine.

The Appeal Board accepted the merits of pen delivery systems and the need to increase awareness of them but that was not the issue.

The Appeal Board noted that bearing in mind European law (in particular the prohibition in the European Directive on the Advertising of Medicinal Products for Human Use) the sole issue for it to determine was whether promotion of NovoPen 3 constituted promotion of prescription only medicines directly to the public contrary to the provisions of Clauses 20.1 and 20.2 of the Code.

The Appeal Board noted that insulin was a prescription only medicine. The NovoPen 3 could only be used with one of eight licensed insulin medicines marketed by Novo Nordisk; Actrapid Penfil, Novorapid Penfil, Insulatard Penfil and Mixtard 10, 20, 30, 40 and 50. It could not be used with insulin marketed by any other manufacturer. This was not unusual.

The Appeal Board noted that the mailing had been distributed to a broad audience comprised of those who had indicated in a consumer survey that somebody in their household had diabetes.

The Appeal Board noted that the NovoPen 3 mailing stated that it was used with insulin cartridges available in all types of human insulin and referred to the cartridges containing 3ml of insulin. The transcript of the patient video stated that Novo Nordisk was 'the only manufacturer to make everything you need for insulin injections: insulin, pens and needles'. Similarly the letter stated that Novo Nordisk '…specialised in the manufacture of insulin and modern insulin injection systems, like NovoPen 3'. The Appeal Board further noted that the brand name of the company's insulin had been airbrushed out of the visual on the mailing. It had not been removed from the video as according to the company representatives the brand name was very small and could not be read.

The Appeal Board considered that if a device could only be used with a specific medicine, or if no other manufacturer's medicine could be used with the device, then promotion of that device would constitute promotion of the medicine and the matter would be covered by the Code. The Appeal Board considered that the mailing and video by referring to the NovoPen 3 constituted promotion of Novo Nordisk's eight insulin medicines to the general public. The Appeal Board upheld the Panel's ruling of a breach of Clause 20.1 of the Code. The materials would direct members of the public towards specific medicines produced by Novo Nordisk and would thus encourage members of the public to ask their doctors to prescribe the NovoPen 3 device and in effect a Novo Nordisk insulin cartridge. The Appeal Board also upheld the Panel's ruling of a breach of Clause 20.2 of the Code. The appeal was unsuccessful.

Following its consideration of this case the Appeal Board noted that the European Commission was at present looking at the EC Directive on the Advertising of Medicinal Products for Human Use to see if it needed amending. The demand for information on medicines was one of the factors that led to the current review. Insulin was a prescription only medicine and it could not legally be advertised to the public. The Appeal Board also noted that the UK regulations prohibited an advertisement to the public that was likely to lead to the use of a relevant medicinal product for the purpose of the treatment, prevention or diagnosis of diabetes and other metabolic diseases.

During its consideration of this case the Appeal Board expressed concern about the letter. It was written on Novo Nordisk company paper and signed by a member of Novo Nordisk's staff. Recipients might gain the impression that the company possessed details about the recipient which was not so. This might adversely affect the relationship between patients and their health professionals. It would have been helpful if the basis of the letter had been explained, ie that it was in response to a consumer questionnaire which the recipient of the letter might not even have completed themselves and that it had been sent by a third party on behalf of Novo Nordisk which did not know the recipients' details. The Appeal Board asked that the company be advised of its views.

Complaint received **20 April 2000**

Case completed **4 August 2000**

CASE AUTH/1024/5/00

NEXSTAR/DIRECTOR v WYETH

Promotion of Abelcet

NeXstar complained about two brochures for Abelcet (amphotericin B lipid complex) issued by Wyeth. NeXstar produced AmBisome (amphotericin in liposomes). An allegation that Wyeth had breached an undertaking and assurance which it had previously given was taken up as a complaint by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

One brochure included the statement '… and helps you balance your budget' supported by a table entitled 'Cost comparison with other lipid-based formulations of amphotericin B'. In this table the recommended daily dose of AmBisome was given as 3mg/kg. NeXstar said that this was incorrect. The dosing stated for AmBisome for the indication in question (severe systemic fungal infections) was: 'Therapy is usually instituted at a daily dose of 1.0mg/kg of body weight, and increased stepwise to 3.0mg/kg, as required.' NeXstar noted that the result of this erroneous information was to overstate the daily cost of AmBisome substantially, thereby appearing to give Abelcet a considerable cost advantage. Only at a patient weight of 60kg did 5mg/kg Abelcet have a lower daily cost than 1mg/kg AmBisome. The brochure compared this 60kg weight but made no reference to the fact that other weights, and especially the standard 'average weight' of 70kg, supported the opposite conclusion with regard to cost. NeXstar alleged a breach of the Code as the statement implied a budgetary advantage over alternative strategies for the management of fungal infection which was inaccurate, unfair and unbalanced and was not supported by the available data. In addition the company alleged a breach of the Code as the table gave an unfair, unbalanced view of the matter with which it dealt. It mis-stated the recommended daily dose of AmBisome and was highly selective in the information presented.

The Panel considered that most readers would assume from the statement and the chart that in patients with severe systemic fungal infections Abelcet was always the least expensive lipid-based amphotericin B formulation. This was not so. Budgets would be set assuming treatment of a wide patient population, not just those weighing 60kg. The Panel considered that the statement and the chart were misleading and breaches of the Code were ruled. The Panel did not consider that the matters at issue were the same as in an earlier case which raised similar issues and ruled that there had been no breach of a previous undertaking.

In the other brochure, NeXstar noted the statement 'At the maximum licensed doses Abelcet is the least expensive of the lipid-based amphotericin B products available.' Whilst factually correct NeXstar said that this was unbalanced and misleading in that it did not refer readers to other approved doses for the available products which did not support the contention, thereby implying that Abelcet had a cost advantage with regard to its competitors. NeXstar alleged a breach of the Code as the statement was unbalanced, unfair and was not based on an evaluation of all the evidence, and therefore misled by implication. The Panel noted that the statement was true. When the maximum dose of a lipid-based amphotericin B product was required, Abelcet was the least expensive option. The claim clearly related only to the use of maximum doses. The Panel did not consider that the claim was misleading. No breach of the Code was ruled.

NeXstar Pharmaceuticals Ltd complained about two promotional items (refs ZABE019/0100 and ZABE031/0999) for Abelcet (amphotericin B lipid complex) issued by Wyeth Laboratories. Both items compared the cost of Abelcet with that of other lipid-based formulations of amphotericin B.

NeXstar stated that it was complaining directly to the Authority as it regarded the matter as a blatant repeat offence despite previous censure in Cases AUTH/860/3/99 and AUTH/943/10/99. Although the precise details of the previous cases were slightly different, they were materially similar insofar as Wyeth had attempted to unfairly establish a claim of superiority for Abelcet over NeXstar's product AmBisome in terms of cost or cost-effectiveness.

The Authority noted that Wyeth had not been involved in Case AUTH/860/3/99, Abelcet being marketed by The Liposome Company at the time. In accordance with advice previously given by the Appeal Board, the allegation of a breach of undertaking was taken up as a complaint by the Director as the Authority itself was responsible for ensuring compliance with undertakings.

A A Balance of Power (ref ZABE019/0100)

COMPLAINT

NeXstar noted that the brochure included the statement '… and helps you balance your budget' supported by a table entitled 'Cost comparison with other lipid-based formulations of amphotericin B'. In this table, the recommended daily dose of AmBisome was given as 3mg/kg. This was incorrect. The dosing statement for AmBisome for the indication in question (severe systemic fungal infections) was: 'Therapy is usually instituted at a daily dose of 1.0mg/kg of body weight, and increased stepwise to 3.0mg/kg, as required.'

NeXstar noted that the result of this erroneous information was to overstate the daily cost of AmBisome substantially, thereby appearing to give Abelcet a considerable cost advantage. At a dose of 1mg/kg/day, using the 28-day treatment period specified in the table, the total cost per patient would be £4,060 for patients up to 50kg in weight and £8,120 for patients up to 100kg in weight, based on a vial cost of £145 (though it should be noted that the price of AmBisome had fallen to £138.48 since the brochure was prepared).

A comparison of 50, 60, 70, 80 and 90kg patients revealed the following:

Patient weight (kg)	Daily cost of Abelcet 5mg/kg	AmBisome 1mg/kg
50	£214	£145
60	£246	£290
70	£296	£290
80	£329	£290
90	£378	£290

This showed that only at a patient weight of 60kg did 5mg/kg Abelcet have a lower daily cost than 1mg/kg AmBisome. The promotional item compared this 60kg weight but made no reference to the fact that other weights, and especially the standard 'average weight' of 70kg, supported the opposite conclusion with regard to cost.

NeXstar alleged a breach of Clause 7.2 of the Code as the statement 'and helps you balance your budget' implied a budgetary advantage over alternative strategies for the management of fungal infection, which was inaccurate, unfair and unbalanced and was not supported by the available data on cost and cost-effectiveness of Abelcet and AmBisome.

In addition the company alleged a breach of Clause 7.6 of the Code as the table gave an unfair, unbalanced view of the matter with which it dealt. It mis-stated the recommended daily dose of AmBisome and was highly selective in the information presented so as to present Abelcet in the best possible light.

RESPONSE

Wyeth stated that it strongly objected to NeXstar's claim that the materials were '… a blatant repeat offence' as this suggested deliberate intent on its part to mislead – this was not the case.

Wyeth stated that following the ruling in Case AUTH/943/10/99 the press release at issue was withdrawn and the relevant product manager asked to review all Abelcet materials for similar cost comparisons, withdraw those which were in breach and amend appropriately. This review was undertaken and the appropriate amendments initiated. Unfortunately the person concerned then left Wyeth's employment without completing all the relevant steps, namely withdrawal of similar items.

Wyeth stated that as a result of these circumstances it was currently reviewing its standard operating procedures of promotional materials. Wyeth stated that it could only apologise for this oversight on its part; the intention was not to deliberately mislead, or to bring the pharmaceutical industry into disrepute. However it had clearly highlighted a deficiency in its internal procedures which it was now addressing as a priority.

PANEL RULING

The Panel noted that the cost comparison chart related to the use of lipid-based amphotericin B in patients weighing 60kg with candidiasis and aspergillosis. The summary of product characteristics (SPC) for Abelcet stated that in patients with severe systemic infections treatment should generally be started at 5mg/kg/day. There was no provision within the SPC for the dose to be increased. The SPC for AmBisome stated that in the treatment of mycosis therapy was usually instituted at a dose of 1mg/kg/day and increased stepwise to 3mg/kg/day as required. The Panel noted that the cost comparison chart compared the daily cost of using the standard dose of Abelcet (5mg/kg/day; £246) with the daily cost of using the maximum dose of AmBisome (3mg/kg/day; £522). The Panel noted that had the cost of the starting dose of AmBisome (1mg/kg/day) been included in the table instead, it would still have been more expensive (£290/day) than Abelcet in patients weighing 60kg; in patients weighing less than or more than 60kg then the starting dose of AmBisome would be the least expensive option.

The Panel noted that the cost comparison chart appeared beneath the statement '… and helps you balance your budget'. The Panel considered that most readers would assume from the statement and the chart that in patients with severe systemic fungal infections Abelcet was always the least expensive lipid-based amphotericin B formulation. This was not so. Budgets would be set assuming treatment of a wide patient population, not just those weighing 60kg. The Panel considered that the statement and the chart were misleading and breaches of Clauses 7.2 and 7.6 were ruled.

The Panel noted that the claim at issue in Case AUTH/860/3/99 was 'Fact: Abelcet is the least expensive lipid based formulation of amphotericin B'; the claim had been ruled in breach of Clause 7.2 of the Code as Abelcet was not always the least expensive lipid-based formulation of amphotericin B. The claim had not been sufficiently qualified as to the basis of the comparison. In Case AUTH/943/10/99 the claim at issue was 'Abelcet is already the most cost-effective lipid-based amphotericin B formulation …'. The Panel did not consider that the two claims were the same; 'least expensive' related only to the purchase cost of a medicine whereas 'cost-effectiveness' included consideration of relative efficacy and incidence of side-effects etc as well as the purchase cost.

The Panel considered that the cost comparison chart and statement now at issue were not the same as the matters considered in either of the previous cases. The cost comparison chart clearly stated the basis on which the comparison had been made and there was no direct claim with regard to cost-effectiveness. The Panel did not consider that the brochure was caught by the undertakings given in the previous cases and no breach of Clause 21 of the Code was ruled in that regard.

B New flexibility (ref ZABE031/0999)

COMPLAINT

NeXstar noted that this brochure included the statement 'At the maximum licensed doses Abelcet is the least expensive of the lipid-based amphotericin B products available.' Whilst factually correct this was unbalanced and misleading in that it did not refer readers to other approved doses for the available products which did not support the contention,

thereby implying that Abelcet had a cost advantage with regard to its competitors.

NeXstar alleged a breach of Clause 7.2 of the Code as the statement was unbalanced, unfair and was not based on an evaluation of all the evidence, and therefore misled by implication.

NeXstar stated that it was particularly concerned at these alleged breaches in view of the precedent of the two recent cases on this very matter. It was clear that Abelcet was being marketed as a lower cost option in the treatment of systemic fungal infections, contrary to any evidence supporting that proposition. NeXstar considered that a letter should be prepared for circulation to relevant doctors and pharmacists making it completely clear that there was no foundation for such claims.

RESPONSE

Wyeth submitted that the statement was factually correct, at maximum doses Abelcet was the cheapest product, the company therefore refuted any suggestion that it was in any way misleading. Wyeth noted that it made no attempt to disguise the reference to dose via lower text/font, or by justifying elsewhere on the page. By stating '… at the maximum licensed doses…' the company was clearly inferring that there was a cost discrepancy at other doses, and was therefore at a loss to see how this statement could appear to be misleading. Wyeth refuted a breach of the Code.

PANEL RULING

The Panel noted that the statement was true, when the maximum dose of a lipid-based amphotericin B product was required, Abelcet was the least expensive option. The claim clearly related only to the use of maximum doses. The Panel did not consider that the claim was misleading. No breach of Clause 7.2 was ruled.

Complaint received **22 May 2000**

Case completed **5 July 2000**

CASE AUTH/1025/5/00 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER v UCB PHARMA

Zirtek 'Dear Doctor' letter

A general practitioner complained about a 'Dear Doctor' letter sent by UCB Pharma. The letter was entitled 'When it comes to children's hayfever, we really do listen' and referred to Zirtek (cetirizine) solution and mentioned that it was a sugar free, banana flavoured children's antihistamine. The letter included a comparison of the cost per day of Zirtek and loratadine. For age 2-6 the cost of Zirtek was given as 15p per day, loratadine for age 2-5 cost 38p per day. Zirtek for age 6+ cost 30p per day and loratadine for age 6-12 cost 76p per day. The letter included a photograph of Zirtek solution surrounded by a bunch of bananas. The complainant alleged that the letter was misleading with regard to the cost of prescribing Zirtek and loratadine as it gave the impression that Zirtek had significant price advantages over loratadine for all age groups. This was not so as loratadine was less expensive than Zirtek in tablet formulation.

The Panel noted that the mailing clearly related to the treatment of hayfever in children and referred only to Zirtek solution. The photograph was of a bottle of Zirtek solution. No mention was made of the presentation of loratadine. The cost comparison chart referred to Zirtek and loratadine in children aged between 2 and 12 and made no mention of the presentation of the products. Clarityn (loratadine) tablets were indicated for use in adults and children of 12 years of age and over. Clarityn syrup was indicated for adults and children over the age of two. Zirtek tablets were indicated for adults and children aged 6 years and over. Zirtek solution was indicated for adults and children over the age of two. Zirtek solution did have a cost advantage over loratadine syrup. The Panel considered that while it would have been helpful to state the dosage forms of Zirtek and loratadine in the cost comparison chart, failure to do so did not amount to a breach of the Code. It was clear from the context of the letter that the cost of Zirtek given in the chart related to the solution formulation. Loratadine tablets were not indicated for use in children under the age of 12, so inclusion of this dosage form in a letter relating to the treatment of hayfever in children would have been inappropriate.

A general practitioner complained about a 'Dear Doctor' letter (ref UCB-Z-00-23) sent by UCB Pharma Limited. The letter was entitled 'When it comes to children's hayfever, we really do listen' and referred to Zirtek (cetirizine) solution and mentioned that it was a sugar free, banana flavoured children's antihistamine. The letter included a comparison of the cost per day of Zirtek and loratadine. For age 2-6 the cost of Zirtek was given as 15p per day, loratadine for age 2-5 cost 38p per day. Zirtek for age 6+ cost 30p per day and loratadine for age 6-12 cost 76p per day. The letter included a photograph of Zirtek solution surrounded by a bunch of bananas.

COMPLAINT

The complainant alleged that the advertisement was misleading with regard to the cost of prescribing Zirtek and loratadine. The complainant considered that the 'Dear Doctor' letter gave the impression that

Zirtek had significant price advantages over loratadine for all age groups. This was not so as loratadine was less expensive than Zirtek in tablet formulation.

RESPONSE

UCB Pharma submitted that the advertisement was extremely specific for Zirtek solution. Zirtek solution was the sole item mentioned in the first and second paragraphs. The third paragraph still referred to the solution only and its flavour. The fourth paragraph referred again specifically to the price of the Zirtek solution and included, together with the table, its daily costs for the two age groups.

UCB submitted that it took great care to make its advertising clear and in keeping with the Code. It was common practice for such price comparisons to be made, and similar ones were used by competitors where it was in their interest to highlight the lower cost of their tablet formulations.

UCB submitted that in this instance it had been a case of misunderstanding on the part of the complainant. In the busy setting of primary care, the company realised that the whole text may not have been read; otherwise it was sure that this complaint would not have arisen.

PANEL RULING

The Panel noted that the mailing clearly related to the treatment of hayfever in children and referred only to Zirtek solution. It consisted of four paragraphs of text, each of which mentioned Zirtek solution. The photograph was of a bottle of Zirtek solution. The first mention of loratadine was in the fourth paragraph. No mention was made of the presentation of loratadine. The cost comparison chart referred to Zirtek and loratadine in children aged between 2 and 12; no mention was made of the presentation of the products.

The Panel examined the summaries of product characteristics (SPCs) for the products. It noted that Clarityn (loratadine) tablets were indicated for use in adults and children of 12 years of age and over (Ref Electronic Medicines Compendium). Clarityn syrup was indicated for adults and children over the age of two. The doses varied depending on the age of the child. Zirtek tablets were indicated for adults and children aged 6 years and over. Zirtek solution was indicated for adults and children over the age of two. Zirtek solution did have a cost advantage over loratadine syrup. The Panel considered that while it would have been helpful to state the dosage forms of Zirtek and loratadine in the cost comparison chart, failure to do so did not amount to a breach of the Code. It was clear from the context of the letter that the cost of Zirtek given in the chart related to the solution formulation. Loratadine tablets were not indicated for use in children under the age of 12, so inclusion of this dosage form in a letter relating to the treatment of hayfever in children would have been inappropriate.

The Panel ruled no breach of Clause 7.2 of the Code.

Complaint received **9 May 2000**

Case completed **11 July 2000**

CASES AUTH/1026/5/00 & AUTH/1027/5/00

CONSULTANT IN PAIN MANAGEMENT v SEARLE and PFIZER

Payment to attend meeting

A consultant in pain management complained about an invitation to a meeting which he had received from Searle and Pfizer. The invitation said that in anticipation of the imminent launch of celecoxib in the UK, the companies would like the complainant to attend a meeting for a small number of secondary care specialists involved in managing arthritis which would take place following the licensing of the product. The aim of the meeting would be to review and discuss information relating to COX-2 specific inhibitor therapy and, primarily, celecoxib. The companies would like the complainant's feedback, advice and help in educating the medical community in the use of this new type of medicine in the management of patients with arthritic diseases. An appropriate honorarium would be paid. The registration form showed that Searle and Pfizer considered it to be a 'training meeting' and it appeared to the complainant that the aim was to enrol doctors in the promotion of this particular medicine and that a fee would be paid for this. The complainant said that it should perhaps be noted that COX-2 specific medicines had been widely discussed in the pain journals and in national and international journals and it was barely conceivable that any doctor involved in the management of inflammatory conditions was not aware of them. In summary, the meeting appeared to offer money to doctors to come to a training meeting in order to have the skills and knowledge to promote this particular medicine. The complainant said that this would seem to be fundamentally different from a focus group meeting, designed simply to gather the opinions of doctors on the potential development of a new device or product.

The Panel accepted that there was a difference between holding a meeting for health professionals and employing health professionals to act as consultants to a company. In principle it was acceptable for companies to pay health professionals and others for advice as to how their products should be promoted. Reference was made to a number of previous cases.

The Panel noted that the purpose of the meeting was to seek input from consultant physicians involved in the management of pain and arthritis about the appropriate information to be included in a series of forthcoming primary care meetings. It was hoped that some of the consultants would agree to chair a local primary care meeting. Eight meetings similar to that complained of had already taken place. Attendance had varied between two and five invitees save one which was attended by eleven. The Panel considered that the small group size and structure of the meetings were such that attendees would have sufficient opportunity to contribute to the meetings as required. The Panel noted that three attendees had agreed to chair subsequent meetings of primary care groups. The invitation stated that the aim of the meeting was to 'review and discuss information relating to COX-2 specific inhibition therapy and primarily celecoxib. We would like your feedback, advice and help in educating the medical community in the use of this new type of drug'. The Panel considered that although the invitation mentioned the interactive nature of the meeting, it was not sufficiently clear about the precise role of invitees, in particular the request to chair subsequent primary care group meetings was not mentioned. The Panel did not consider that there was sufficient justification for the number of meetings held. The potential delegates had been identified by Searle's representatives. Such a selection process could be open to criticism. The delegates were being 'employed' as consultants and as such their inclusion should stand up to independent scrutiny. The Panel considered that it was difficult in such cases to decide precisely where the boundary lay. The Panel was concerned about the wording of the invitation and the number of meetings held. On balance the Panel considered that the arrangements meant that they constituted a series of promotional meetings. It was not appropriate to pay doctors to attend such meetings. A breach of the Code was ruled.

A consultant in pain management complained about an invitation to a meeting which he had received from Searle and Pfizer Limited. The invitation said that in anticipation of the imminent launch of celecoxib in the UK, the companies would like the complainant to attend a meeting for a small number of secondary care specialists involved in managing arthritis which would take place following the licensing of the product. The aim of the meeting would be to review and discuss information relating to COX-2 specific inhibitor therapy and, primarily, celecoxib. The companies would like the complainant's feedback, advice and help in educating the medical community in the use of this new type of medicine in the management of patients with arthritic diseases. An appropriate honorarium would be paid. Material would be presented in slide format by a consultant rheumatologist and the meeting would run approximately 14.00 hrs to 18.00 hrs. The invitation was accompanied by a list of thirteen dates and venues for the UK speaker training days together with a registration form which participants were to complete giving two available dates.

COMPLAINT

The complainant stated that the registration form showed that Searle and Pfizer considered it to be a 'training meeting' and it appeared to the complainant that the aim was to enrol doctors in the promotion of this particular medicine and that a fee would be paid for this. It should perhaps be noted that COX-2 specific medicines had been widely discussed in the pain journals and in national and international journals and it was barely conceivable that any doctor involved in the management of inflammatory conditions was not aware of them. In summary, the

meeting appeared to offer money to doctors to come to a training meeting in order to have the skills and knowledge to promote this particular medicine. This would seem to be fundamentally different from a focus group meeting, designed simply to gather the opinions of doctors on the potential development of a new device or product.

RESPONSE

Searle responded on behalf of both itself and Pfizer.

Searle stated that following marketing authorization for Celebrex, the companies' intention had been to run a series of meetings for a primary care audience. The objective of the meetings was to present information on COX-2 inhibitors and discuss their place in the management of arthritis, against the background of the disease epidemiology and the ongoing changes within the primary care setting. The meetings would be scientific and educational in content, but as they would include presentation of data pertaining to celecoxib they might also be regarded as promotional.

None of these primary care meetings had yet taken place, and before initiating them the companies wanted to ensure that the information to be presented at them was appropriate and relevant for the intended audience. To this end it was decided to set up a series of meetings with consultant physicians involved in the management of pain and arthritis, to seek their input into the most appropriate information to be included.

A small number of UK consultants (thirteen) who were previously familiar with the clinical data on celecoxib from their involvement in advisory panels, clinical trials, etc, agreed to present a core set of slides prepared by Searle and Pfizer to their colleagues and seek feedback for the companies on the slides' suitability (or otherwise) for a primary care audience and on any additional or alternative information that should be included. There would be particular emphasis on which data would be of the greatest value to generalists or primary care physicians, many of whom would not (yet) be familiar with COX-2 technology from either journals or other meetings. It was also hoped that some of the consultants attending the meeting would agree to chair a primary care meeting in their local area.

The complainant had received an invitation to one of these secondary care advisory meetings, at which his/her feedback would be sought. As the companies were seeking advice from the attendees, it was considered appropriate to offer an honorarium (£350) for this service, since the attendees would, in effect, be acting as consultants to Searle and Pfizer.

Searle stated that although the meetings were advisory, as they were to lead onto further meetings of at least a semi-promotional nature, it was considered appropriate to hold the meetings only after marketing authorization for Celebrex was obtained, when the licensed indications and other relevant particulars would be clear. Celebrex was licensed in the UK on 2 May 2000.

In its letter, the Authority had asked for information on the number of invitees/attendees at the meetings, their areas of expertise and how they were chosen. A potential list of consultant physicians involved in the management of arthritis (rheumatologists, anaesthetists, geriatricians) had been developed over the last few months from the companies' knowledge of the therapeutic area. With thirteen consultants willing to run the advisory meetings, a provisional list of dates for them to chair one meeting each was agreed. Between ten and fifteen consultants were invited to attend each meeting.

Searle stated that to date, three meetings had taken place with five or six attendees at each meeting, in addition to the chairman and Searle or Pfizer personnel (a member of Searle's medical staff had attended two of these meetings). Prior to the meeting the attendees received an invitation letter and details of proposed dates of other meetings (in case they wished to attend but could not manage the specified date). The meetings had taken place in the morning or afternoon with a buffet lunch and/or coffee. No other hospitality had been provided.

The only material provided to delegates at the meetings had been paper copies of the PowerPoint clinical core slide set developed by Searle and Pfizer, a copy of which was provided.

In summary, Searle and Pfizer were organising a series of advisory meetings with consultant physicians involved in the management of arthritis to seek their input and advice on developing a meetings programme for Celebrex in primary care. The companies believed that the number of consultants invited/attending these advisory meetings was suitable and proper in view of the need to educate primary care physicians nationwide on COX-2 technology and Celebrex, most appropriately by local specialists familiar with the practices, interests and attitudes of the particular locality. The companies also believed the level of the honorarium to be commensurate with the professional advice to be provided over a half-day meeting in each case.

For these reasons Searle or Pfizer did not believe that they had breached the Code in any respect in connection with these advisory meetings.

In response to a request for further information Searle stated that the potential list of consultant physicians was originally developed by Searle some two years ago, based on feedback from the field force, then promoting Arthrotec and Zydol, on the opinion and thought leaders in their regions. The list was formally reviewed with members of the field force in September 1999 and a copy of the memo that was sent out for this purpose was provided. The list was reviewed by Pfizer but developed by Searle. All the consultants identified were originally invited to one of the planned meetings.

As the meetings were to be led by one of the consultant physicians who was familiar with the celecoxib clinical data, the final agenda for the individual meetings was their decision. A proposed agenda was made available but could be amended. The proposed agenda for a meeting planned to last about four hours suggested an hour or more to review and discuss the clinical slides and one and a half hours to discuss and feedback on the information required by Primary Care Groups.

Searle noted that it had originally stated that three meetings had taken place. This was incorrect. Six meetings had taken place by 19 June. Details of these were provided.

The latter two meetings in London and Manchester were organised and run by the chairing consultant physician and feedback from the meetings was awaited. The feedback for the first meeting on 30 May, produced by the chairman of the meeting, was provided. The second meeting on 2 June in Glasgow was attended by a member of Searle's medical staff and a copy of his minutes of the meeting was provided together with the feedback from the third and fourth meetings on 9 June. For one of these meetings the feedback was provided by the chairman consultant and for the other by the Searle medical group attendee; the agenda for this meeting was also enclosed as it expanded the original proposed agenda to include a session on communication skills delivered by an external company.

Searle confirmed that there was no formalised process across the series of meetings in terms of standard questions, etc, but rather a discussion of the data presented and how well the various slides delivered information and what should be changed or added to.

Searle stated that in view of this pending complaint there had been limited contact with meeting attendees since their attendance. To date, three of the attendees had agreed to speak and/or chair a primary care meeting in their local area as a follow-up to their attendance.

The Panel had also asked if there was sufficient regional variation in the management of arthritis to justify the number of meetings. Pain was the major feature of arthritis. Searle referred to the Clinical Standards Advisory Group (CSAG) summary report on services for NHS patients with acute and chronic pain, published in March 2000, which found 'professional differences lead to a wide range of treatments' and a marked variation in the level and nature of specialist services for acute and chronic pain. However the main purpose of the celecoxib meetings was not to explore regional variations in the management of arthritis, but to discuss the data on a new product with a substantial group of UK thought leaders and seek their input on the appropriate information for a primary care audience. The role of COX-2 inhibitors in the management of arthritis had yet to be established. For the management of osteoarthritis the current Prodigy guidelines advised 'New NSAIDs that selectively inhibit COX-2 are effective and may have fewer adverse reactions but clinical experience is required before recommendation'. The advice from the Primary Care Rheumatology Society (vol 10, Feb 2000) made no reference to COX-2 inhibitors.

Searle confirmed that six meetings took place before its initial response of 19 June. Two further meetings had been held on 7 July in London and 12 July in Coventry, based on the original interest expressed by invitees. The feedback from the meetings held so far had been useful and relatively consistent and the Searle medical department was currently producing revised clinical slides for further use at education meetings.

The intention was to complete these meetings by early July to enable feedback to be incorporated and no further meetings of this nature were planned by either Searle or Pfizer.

PANEL RULING

The Panel accepted that there was a difference between holding a meeting for health professionals and employing health professionals to act as consultants to a company. In principle it was acceptable for companies to pay health professionals and others for advice as to how their products should be promoted. The arrangements had to comply with the Code.

The Panel noted that there had been a number of previous relevant cases. Case AUTH/471/10/96 involved a single focus group meeting. On that occasion the Panel had had some concerns about the meeting. It noted that those attending the meeting had been invited to act as consultants to the company and the number of delegates had been limited thus ensuring that all could make a contribution to the proceedings. On balance an honorarium of £200 had not been unreasonable for the amount of work involved. The hospitality had been acceptable. No breach of the Code was ruled. A subsequent case (Case AUTH/686/3/98) concerned ten similar meetings in various locations around the UK. An honorarium of £200 had been offered. In the Panel's view it was questionable whether the attendees would have truly acted as consultants each giving advice to justify such an honorarium and reimbursement of travel expenses. There had not been sufficient justification regarding regional variations in the management of the condition at issue to support the number of meetings held. A breach of Clause 18.1 of the Code had been ruled. This had been upheld on appeal to the Appeal Board which had noted that places were allocated on a first come, first served basis. In the Appeal Board's view there had not been sufficient targeting of the invitations. Another previous case (Case AUTH/944/10/99) concerned one of a series of seven meetings for which the attendees would receive an honorarium of £350. The Panel accepted that there was sufficient clinical justification for the number of meetings held. The chairperson had been chosen by the sponsoring company but the delegates had been chosen by the chairperson. The Panel had some concerns about the meeting but decided on balance that the company was employing health professionals to act as consultants and in that regard the Panel accepted that the honorarium was a genuine payment for advice. Although on the borderline it was not unreasonable for the amount of work involved. No breach of the Code was ruled in that regard. A breach was ruled in that case as the letter of invitation made no mention that the recipient was being invited to act as a consultant.

Turning to the present case the Panel noted that the purpose of the meeting was to seek input from consultant physicians involved in the management of pain and arthritis about the appropriate information to be included in a series of forthcoming primary care meetings. It was hoped that some of the consultants would agree to chair a local primary care meeting.

The Panel noted that the agenda could be varied by the chairman, but a typical meeting would last from 13.00 hours until 17.30 hours. Following an introduction there would be a slide presentation and discussion section lasting 1 hour 20 minutes followed by a 30 minute syndicate group session. The meeting would finish with a one hour reporting back session from the syndicate groups, followed by a half hour lecture about presentation technique. The Panel examined copies of the slides presented which discussed NSAID use and pharmacology, COX-2 discovery and, with reference to Celecoxib, its clinical pharmacology and effect on platelet function, its efficacy in osteoarthritis and rheumatoid arthritis, gastrointestinal safety and its overall safety profile and tolerability. The final slide concluded that 'celecoxib should be considered first after ibuprofen in OA and RA'.

The Panel noted that eight meetings had already taken place, attendance had varied between two and five invitees save one which was attended by eleven. The Panel noted the feedback documents provided and noted these provided comments on data presented and suggested amendment where appropriate. The Panel noted that a meeting on 2 June had been attended by four invitees and three Searle personnel. The Panel considered that the small group size and structure of the meetings were such that attendees would have sufficient opportunity to contribute to the meetings as required. The Panel noted that three attendees had agreed to chair subsequent meetings of primary care groups.

The Panel noted that the invitation stated that the aim of the meeting was to 'review and discuss information relating to COX-2 specific inhibition therapy and primarily celecoxib. We would like your feedback, advice and help in educating the medical community in the use of this new type of drug'. The Panel considered that although the invitation mentioned the interactive nature of the meeting, it was not sufficiently clear about the precise role of the invitees, in particular the request to chair subsequent primary care group meetings was not mentioned. The Panel noted the Clinical Standards Advisory Group summary report on the variation in the nature and level of specialist services and Searle's submission that the main purpose was not to explore regional variations in the management of arthritis. The Panel did not consider that there was sufficient justification for the number of meetings held. The Panel also noted that the potential delegates had been identified by Searle's representatives. Such a selection process could be open to criticism. The delegates were being 'employed' as consultants and as such their inclusion should stand up to independent scrutiny.

The Panel considered that it was difficult in such cases to decide precisely where the boundary lay. The Panel was concerned about the wording of the invitation and the number of meetings held. On balance the Panel considered that the arrangements for the meetings meant that they constituted a series of promotional meetings. It was not appropriate to pay doctors to attend such meetings. The Panel ruled a breach of Clause 18.1 of the Code.

Complaint received **31 May 2000**

Case completed **10 August 2000**

CASE AUTH/1028/6/00

DIRECTOR v SCHERING HEALTH CARE

Breach of undertaking

Schering Health Care advised the Authority that an advertisement for Cyprostat (cyproterone acetate) had appeared in the May 2000 edition of the British Journal of Urology International in breach of its undertaking given in Case AUTH/878/5/99. The Director of the Authority decided that the matter was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code. This was consistent with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review.

The Panel considered that, although different, the claim in the advertisement was sufficiently similar to the claim in Case AUTH/878/5/99 for it to be caught by the undertaking given in that case. Schering Health Care had thus failed to comply with its undertaking. A breach of the Code was ruled as acknowledged by Schering Health Care.

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 the future. It was important for the reputation of the industry that companies complied with undertakings. Case AUTH/878/5/99 had been completed in July 1999. Following its acceptance of the Panel's ruling in that case, Schering Health Care had issued instructions that all current materials should be destroyed. The company's advertising agency had recalled the film plates from the British Journal of Urology and destroyed them. The advertisement that had recently been published had been generated from some old plates, left with the journal by a previous agency, which had not been destroyed. Letters from Schering Health Care's advertising agency were provided which stated that the out of date advertisement had appeared because an internal administrative error had led to the supply of incorrect copy instructions.

The Panel noted that Schering Health Care had had procedures in place to ensure compliance with the undertaking. The advertisement at issue had been published ten months after the completion of the previous case due to the use of a film plate that had been left with the journal by the previous advertising agency. Nonetheless Schering Health Care had to bear responsibility under the Code. Noting that the company had taken steps to comply with the undertaking the Panel did not consider that the circumstances constituted a breach of Clause 2 and no breach of that clause was ruled. In the Panel's view, companies would be well advised to have procedures in place to ensure that when they changed agencies all material generated by the old agency, whether still with the agency or with a third party, was returned to the company.

COMPLAINT

Schering Health Care Limited advised the Authority that an advertisement for Cyprostat (cyproterone acetate) had appeared in the May 2000 edition of the British Journal of Urology International in breach of its undertaking given in Case AUTH/878/5/99.

The Director of the Authority decided that the matter was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code. This was consistent with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review. The Authority requested that, when considering the matter, Schering Health Care should bear in mind the provisions of Clauses 2, 9.1 and 21 of the Code.

RESPONSE

Schering Health Care stated that Clause 21 appeared to be unequivocal in that it required the company to ensure that it complied with any undertaking which had been granted. This apparently absolute obligation had not been fulfilled and the company accepted that, on a strict interpretation of the Code, Clause 21 had been breached. However, Schering Health Care noted that companies were to abide by the letter and spirit of the Code and it considered that, by extension, this meant that it should be interpreted in a purposive manner. Accordingly, while the company appeared to have breached the letter of the Code, it requested that the circumstances under which the material was published were considered.

Schering Health Care stated that the material had been published inadvertently due to an error on the part of its advertising agency, and correspondence was provided to substantiate this. The company stated that following the Panel's ruling in Case AUTH/878/5/99, it issued instructions that all current materials should be destroyed. Its advertising agency consequently recalled its advertising film plates from the British Journal of Urology and then destroyed them. However, the journal had some old plates from a previous agency which were not destroyed and these were the ones which were used in the advertisement which was the subject of the complaint.

Schering Health Care considered that it took all reasonable steps to comply with the undertaking and the Code but an unusual set of circumstances, involving publishers with whom it had no direct relationship, had led to the offending material appearing. The company stated that it had taken steps to ensure that when it changed agencies in future, all old material would be recalled from publishers.

With regard to Clause 2, Schering Health Care noted that it was a sign of particular censure and it considered that it would be excessive in this case to find the company in breach of this clause. It fully accepted that the breach of an undertaking was a serious matter and it accepted that, had the publication of the offending material been deliberate or the result of indifference to the requirements of the Code, then a finding of a breach of Clause 2 might be

justified. However, as mentioned above, the publication was an error on the part of the advertising agency and Schering Health Care noted that it had brought the matter to the attention of the Authority as soon as it became aware of the publication. The company had also taken steps to avoid a recurrence.

Schering Health Care noted that Clause 9.1 of the Code required high standards to be maintained at all times. The company submitted that it did maintain high standards at all times but that this did not eliminate the possibility that errors might occur from time to time. This was an isolated incident and it had taken steps to improve its internal procedures to avoid a recurrence.

PANEL RULING

The Panel noted that in Case AUTH/878/5/99 it had been its view that the claim 'Cyprostat is an effective monotherapy for the long-term palliative care of prostate cancer patients', implied that the product could be used in all prostate cancer patients which was not so. The summary of product characteristics (SPC) stated that the product could be used only when LHRH analogues or surgery were contraindicated, not tolerated or where oral therapy was preferred. The claim was too general given the licensed indication. A breach of the Code was ruled.

The Panel noted that the advertisement now at issue contained the claim 'monotherapy'. The Panel considered that this too was a broad claim and not qualified with regard to the patient population in which it could be used as monotherapy. The Panel considered that, although different, the claim was sufficiently similar to the claim in Case AUTH/878/5/99 for it to be caught by the undertaking given in that case. Schering Health Care had thus failed to comply with its undertaking. A breach of Clause 21 was ruled as acknowledged by Schering Health Care.

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 the future. It was important for the reputation of the industry that companies complied with undertakings.

The Panel noted that Case AUTH/878/5/99 was completed in July 1999. Schering Health Care had submitted that following its acceptance of the Panel's ruling in that case it had issued instructions that all current materials should be destroyed. The company's advertising agency consequently recalled its film plates from the British Journal of Urology and then destroyed them. The Panel noted that the advertisement that had recently been printed had however been generated from some old plates, left with the journal by a previous agency, which had not been destroyed. Letters from Schering Health Care's advertising agency were provided which stated that the out of date advertisement had appeared because an internal administrative error had led to the supply of incorrect copy instructions.

The Panel noted that Schering Health Care had had procedures in place to ensure compliance with the undertaking given in Case AUTH/878/5/99. The advertisement at issue had been printed ten months after the completion of the previous case due to the use of a film plate that had been left with the journal by Schering's previous advertising agency. Nonetheless Schering Health Care had to bear responsibility under the Code. Noting that the company had taken steps to comply with the undertaking the Panel did not consider that the circumstances in the case now before it constituted a breach of Clause 2 and no breach of that clause was ruled.

The Panel noted the circumstances that had led to the use of an out-of-date advertisement. In the Panel's view companies would be well advised to have procedures in place to ensure that when they changed agencies all material previously generated by the old agency, whether still with the agency or with another third party, was returned to the company.

Complaint received **1 June 2000**

Case completed **21 July 2000**

NOVARTIS v FUJISAWA

Prograf journal advertisement

Novartis complained about a journal advertisement for Prograf (tacrolimus) which had been issued by Fujisawa. An introductory paragraph stated that 'Previous large multicentre studies comparing tacrolimus with the original formulation of ciclosporin in kidney transplantation have shown tacrolimus to be significantly better in terms of preventing acute, corticosteroid-resistant and vascular rejection, and in liver transplantation, was associated with significantly lower rates of acute, refractory acute and chronic rejection, as well as numerically higher patient and graft survival'. The advertisement also stated that major trials comparing tacrolimus with the microemulsion formulation of ciclosporin in renal and hepatic transplantation had been presented in May at the Annual meeting of the American Society of Transplantation and the American Society of Transplantation Physicians and the body of the advertisement discussed the data presented. Novartis had marketed the original formulation of cyclosporin, Sandimmun. This was still licensed and available on a named patient basis. Sandimmun concentrate for infusion was also still available. The oral version currently available was Neoral which was a pre-concentrated formulation of cyclosporin which underwent a microemulsification process in the presence of water.

Novartis was concerned that six references cited to support the comparative efficacy claims used doses and dosage regimes outside of the licensed recommendations for Sandimmun. For example, Mayer *et al* (1997) used a dose of 4mg/kg/bd Sandimmun, started within 24 hours of surgery. However, the recommended licensed dosage regime was 10 to 15mg/kg body weight given 4 to 12 hours prior to transplantation. Treatment should then be continued at a dose of 10 to 15mg/kg per day for one to two weeks post-operatively. Dosage should then be gradually reduced until a maintenance dose of 2 to 6mg/kg per day was reached. The same study used the maximum recommended dose for tacrolimus (0.15mg/kg bd) as the comparative treatment. Novartis noted that Pirsch *et al*, Pichlmayr *et al* and Weisner *et al* also used cyclosporin doses lower than the initial, recommended licensed dose. Vanrenterghem *et al* and Busuttil and Holt were summary articles referring to the data presented by Pirsch *et al*, Pichlmayr *et al*, and Weisner *et al*. Novartis did not consider on this basis that these studies represented fair comparisons and it was thus in breach of the Code to use them to support comparative efficacy claims. Indeed, the use of Pirsch *et al* and Pichlmayr *et al* to substantiate relative efficacy claims for tacrolimus had already been the subject of a previous ruling (Case AUTH/513/2/97). In that instance, a breach of the Code was ruled.

The Panel noted that transplantation was a complex therapy area. Clinicians using the various medicines would be experts in their field. Clinicians might use doses of products outside the licensed recommendations. The Panel noted Fujisawa's submission that, while in initial trials cyclosporin was used as a single agent, today it was usually administered in conjunction with other immunosuppressants. Combination therapy meant that low doses of cyclosporin could be used thus reducing the risk of renal toxicity. The Panel noted that the references cited all used cyclosporin as part of triple or quadruple therapy. The Sandimmun summary of product characteristics (SPC) gave details of the doses to be administered when the product was to be used as a single agent ie oral treatment should be initiated at 10 to 15mg/kg/day 4 to 12 hours before transplantation continuing for one to two weeks post operatively reducing gradually to a maintenance dose of 2 to 6mg/kg/day. These were the doses cited by Novartis in its complaint. With regard to combination therapy, however, the SPC stated that lower doses could be used and gave, as an example of this, 3 to 6mg/kg/day initially. In the Panel's view, such a dose range, given as an example, was for guidance only and not to be regarded as definitive. The SPC also stated that dosage should be adjusted according to cyclosporin blood levels or to serum creatinine and urea levels. The Panel noted that there would be inter- and intra-patient variation in the pharmacokinetics and pharmacodynamics of cyclosporin and that therapy could be tailored by careful assessment of each patient. The Panel also noted that the iv dose for patients unable to take oral therapy was one third of the recommended oral dose. Patients should be transferred to oral therapy as soon as the given circumstances allowed.

The Panel noted that in Case AUTH/513/2/97 Fujisawa had submitted that although the cyclosporin dosage might not mirror the SPC dosage, the studies did reflect the use of the product in major transplant centres in the UK. The Panel had ruled that the dose of Sandimmun used in the cited studies was less than the licensed dose which was unfair and a breach of the Code was ruled. The Panel considered that the present case was different to the previous case as Fujisawa had not included in its submission that the dosage regimens in the Sandimmun SPC were recommendations and were not prescriptive. That particular issue had thus not been considered.

In the case now before it, the Panel considered that, on balance, the studies cited did not represent an unfair comparison of Prograf and Sandimmun. According to current clinical practice cyclosporin was likely to be used as part of triple or quadruple therapy where doses could be kept low to avoid toxicity. The wording of the SPC was such that the dose range stated for such therapy was not prescriptive and treatment should be tailored to meet individual needs. No breach of the Code was ruled.

Upon appeal by Novartis, the Code of Practice Appeal Board noted that transplantation was a highly specialised and complex area. Clinicians using the various medicines would be experts in the field. The Appeal Board noted the submission from

Fujisawa that cyclosporin was usually administered with other immunosuppressants. The Appeal Board noted the section of the Sandimmun SPC headed 'Dosage and administration' which stated that 'When Sandimmun is given with other immunosuppressants (eg corticosteroids or as part of a triple or quadruple drug therapy) lower doses (eg 3-6mg/kg/day orally initially) may be used'. The Appeal Board noted that various pharmacokinetic and pharmacodynamic factors needed to be taken into account when administering Sandimmun or Prograf which would influence the dosage regimen post transplant with dosing tailored to meet individual needs. Transplant specialists would be familiar with these clinically important factors.

The Appeal Board noted the views expressed by the Fujisawa representatives regarding the studies. Prograf was compared with the best Sandimmun based regimen. The representatives stated that the use of pre-transplant doses of Sandimmun varied. Most transplant centres in Europe did not use pre-transplant doses. Steroid loading doses were used. US centres did use pre-transplant doses. A comment was made that the population mix was different in the US to Europe. Clinical practice was to base immunosuppressive therapy on monitoring of blood levels and the overall clinical condition of the patient. Interpatient variability meant that dosing needed to be individualised on a patient by patient basis. The Appeal Board noted that the doses of Sandimmun used in the studies were not outside the Sandimmun SPC. The product was administered with cortiscosteroids as part of triple or quadruple therapy. The best Sandimmun based regimen had been used in the studies. The Appeal Board noted that the studies had been used for registering Prograf in Europe and the US. The Appeal Board upheld the Panel's ruling of no breach of the Code.

Novartis Pharmaceuticals UK Ltd complained about an advertisement (ref 0174/GCC) for Prograf (tacrolimus) which had been issued by Fujisawa Limited and published in The Lancet, 20 May 2000. An introductory paragraph stated that 'Previous large multicentre studies comparing tacrolimus with the original formulation of ciclosporin in kidney transplantation have shown tacrolimus to be significantly better in terms of preventing acute, corticosteroid-resistant and vascular rejection, and in liver transplantation, was associated with significantly lower rates of acute, refractory acute and chronic rejection, as well as numerically higher patient and graft survival'. The advertisement also stated that major trials comparing tacrolimus with the microemulsion formulation of ciclosporin in renal and hepatic transplantation had been presented in May at the Annual meeting of the American Society of Transplantation and the American Society of Transplant Physicians and the body of the advertisement discussed the data presented.

Novartis had marketed the original formulation of cyclosporin, Sandimmun. This was still licensed and available on a named patient basis. Sandimmun concentrate for infusion was also still available. The oral version currently available was Neoral which was a pre-concentrated formulation of cyclosporin which underwent a microemulsification process in the presence of water.

COMPLAINT

Novartis alleged that the advertisement was in breach of Clause 7.2 of the Code. The introductory paragraph made numerous comparative efficacy claims relating to Prograf and Sandimmun (cyclosporin). Novartis was concerned that six references (Pirsch *et al* 1997, Pichlmayr *et al* 1997, Weisner *et al* 1998, Mayer *et al* 1997, Vanrenterghem *et al* 1999 and Busuttil and Holt 1998) cited to support these claims used doses and dosage regimes outside of the licensed recommendations for Sandimmun. For example, Mayer *et al* (1997) used a dose of 4mg/kg bd Sandimmun, started within 24 hours of surgery. However, the recommended licensed dosage regime was 10 to 15mg/kg body weight given 4 to 12 hours prior to transplantation. Treatment should then be continued at a dose of 10 to 15mg/kg per day for 1 to 2 weeks post-operatively. Dosage should then be gradually reduced until a maintenance dose of 2 to 6mg/kg per day was reached. The same study used the maximum recommended dose for tacrolimus (0.15mg/kg bd) as the comparative treatment.

Novartis noted that Pirsch *et al*, Pichlmayr *et al* and Weisner *et al* also used cyclosporin doses lower than the initial, recommended licensed dose. Vanrenterghem *et al* and Busuttil and Holt were summary articles referring to the data presented by Pirsch *et al*, Pichlmayr *et al*, and Weisner *et al*.

Novartis did not consider on this basis that these studies represented fair comparisons and it was thus in breach of Clause 7.2 of the Code to use them to support comparative efficacy claims. Indeed, the use of Pirsch *et al* and Pichlmayr *et al* to substantiate relative efficacy claims for tacrolimus had already been the subject of a previous ruling (Case AUTH/513/2/97). In that instance, a breach of Clause 7.2 was ruled.

Novartis provided copies of intercompany correspondence regarding the use of the studies in promotional items. Fujisawa gave assurances that new material would not include anything which, in its opinion, was in breach of the Code. Novartis stated that despite this assurance, however, the advertisement in question had now been published and appeared to form part of a new advertising campaign. Despite protracted dialogue with Fujisawa, it intended to continue to use these data to substantiate misleading comparative efficacy claims, even though this was previously ruled as being in breach of Clause 7.2 of the Code (Case AUTH/513/2/97)

RESPONSE

Fujisawa did not agree that its comparative efficacy statements were in breach of the Code; they formed an accurate, balanced, fair and objective comparison of Prograf and Sandimmun.

Fujisawa stated that although the Pirsch and Pichlmayr studies had been at issue in Case AUTH/513/2/97, the context in which they were used then was very different to that of the present

context whereby the whole theme and emphasis was entirely different. The company had undertaken a detailed investigation and had looked closely at each study in terms of its design, dosing regimen, etc. and had compared all these elements with the recommendations made in the Sandimmun summary of product characteristics (SPC).

Fujisawa stated that the area of immunosuppression in organ transplantation was a highly specialised and complicated one with regards to the influence of the various pharmacokinetic and pharmacodynamic factors that needed to be taken into consideration when administering Prograf or Sandimmun in order to achieve optimal outcomes. Due to the potential for inter- and intra-patient variability in drug absorption, clearance with time as well as the confounding factors such as the patient's clinical condition and concurrent medications being taken, these clinically important factors influenced the dosing regimen of either of these medicines. In transplant patients dosing was individualised to achieve optimal outcomes with minimum complications. The transplant specialists were very familiar with these clinically important factors and were able to individualise the dosing regimen to suit each patient.

Fujisawa stated that Sandimmun was introduced clinically in 1978 and in initial trials it was used as a single agent at higher doses, but its side effects led to a reduction in its dose while maintaining immunosuppression by combination therapy with corticosteroids. This resulted in the evolution of triple therapy, where lower doses of cyclosporin were used in combination with azathioprine and corticosteroids to reduce the cyclosporin-related toxicity. This was currently the most widely used protocol for immunosuppressive therapy and was acknowledged in the Sandimmun SPC which stated in the 'Precautions' section; 'However, some transplant centres use Sandimmun together with azathioprine and corticosteroids or other immunosuppressive agents (all in low doses) with the aim of reducing the risk of Sandimmun induced renal dysfunction or renal structural changes. When it is used with other immunosuppressive agents, there is a risk of over immunosupression, which can lead to increase susceptibility to infection and to possible development of lymphoma'.

Fujisawa explained that another progression from triple therapy had been quadruple therapy with the addition of antibodies (ie ALG) for the first 14 days. This evolutionary process had resulted in the use of different cyclosporin-based immunosuppressive regimens in different transplantation centres. These regimens continued to evolve even today. Furthermore, inter- and intra-patient variability in efficacy and tolerance to the immunosuppressive regimen used had led to the individualisation of therapy aided by determining blood concentrations of cyclosporin. Moreover the inter-patient variability in bioavailability made the prediction of the relationship between the administered dose and the systemic availability difficult. For these reasons only the initial dose was recommended. Therapy based on clinical judgement aided by measurement of drug concentrations in blood was recommended thereafter.

It was well accepted in the area of transplantation that the initial oral dosing (ie based on mg/kg) of Prograf or Sandimmun were only recommendations and were intended to act as a guideline. The doses of these agents were then adjusted based on clinical judgement and by measuring blood levels of cyclosporin or tacrolimus. Doses were adjusted in the event of adverse effects of medicine(s) (suspicion of toxicity), blood levels being below or above the therapeutic range, interactions, side-effects, rejection and the clinical condition of the patient. Hence in transplantation, immunosuppressive therapy with either agent was based on monitoring of blood levels and taking into consideration the overall clinical condition of the patient.

Fujisawa noted that the Sandimmun and the Prograf SPCs contained numerous statements in virtually every section on the need and importance of adjusting the dosages (initial or maintenance does) of these agents due to a number of clinically important factors. In particular the Sandimmun SPC stated, under 'Dosage and Administration', 'Dosage should be adjusted by monitoring cyclosporin blood levels and kidney function (see 'Further Information' and 'Precautions'). Under 'Precautions', the SPC stated 'Sandimmun can impair renal function. Close monitoring of serum creatinine and urea is required and dosage adjustment may be necessary. Increases in serum creatinine and urea occurring during the first few weeks of Sandimmun therapy are generally dose dependent and reversible and usually respond to dose reduction' and 'Sandimmun may also affect liver function and dosage adjustment, based on the results of bilirubin and liver enzymes monitoring, may be necessary'.

Fujisawa noted that in the clinical trial setting both of the above precautions were of relevance as a patient's renal or liver function might often be compromised and the transplant physician would adjust the initial dosage accordingly. In addition pre-operative impairment needed to be considered when administering Sandimmun under this setting.

Under 'Drug Interactions' it was stated that 'Care should be taken when using Sandimmun in combination with systemic antibiotics or other compounds known to have nephrotoxic effects, eg … aminoglycosides, … Various agents are known to either increase or decrease the plasma or whole blood levels of cyclosporin …'. 'In transplant patients, frequent measurements of cyclosporin, and if necessary, Sandimmun dosage adjustment is required, particularly during the introduction or withdrawal of co-administered drugs'.

Again, in the clinical trial or non-clinical trial setting, co-administration of medicines was employed, which could affect the levels of cyclosporin, which would require either dose reduction or increase in dose of Sandimmun.

The 'Side effects' section stated 'Side-effects are usually dose dependent and responsive to dose reduction'.

Fujisawa stated that to further demonstrate this point, the Prograf SPC made similar statements, for example, under section 4.2 'Posology and Method of

Administration' 'The dosage recommendations given below for oral administration are intended to act as a guideline'. 'Only initial dosing is recommended and therefore therapy should be based on clinical judgement aided by measurement of tacrolimus concentrations in blood' and under 'Dosage Level Recommendations', 'Initial dose level recommendation'. As could be seen only a recommendation of the initial starting dose was made. Under 'Compromised Patients' the SPC stated 'A dose reduction may be necessary in patients with pre- and/or post operative impairment' (ie liver or renal function).

Fujisawa stated that the main interpretation which could be drawn from the SPCs was that the initial oral dosing was only a recommendation to act as a guideline. Doses of either medicine were adjusted for each patient by monitoring cyclosporin or tacrolimus blood levels (to be within the specified therapeutic range) and based upon the clinical condition of the patient.

With regard to the studies by Pichlmayr *et al*, Weisner *et al*, Pirsch *et al* and Mayer *et al*, Fujisawa noted that they had all been approved by the various Health Authorities in the respective countries (Medicines Control Agency in the case of UK) and independent review boards (Ethics Committees of the institutions). As stated in the study protocols, Prograf was compared with best Sandimmun-based regimen (as each institution had had nearly 10 years of experience in using Sandimmun) at each institution ensuring that the design would result in the control group to be comparable to the highest success rate at that institution.

Fujisawa noted that the Sandimmun SPC was very clear in the 'Dosage and administration' section which stated: 'When Sandimmun is given with other immunosuppressants (e.g. with corticosteroids or as part of a triple or quadruple drug therapy) lower doses (e.g. 3 to 6mg/kg/day orally initially) may be used'. Fujisawa explained that triple therapy meant: Sandimmun + corticosteroids + azathioprine and quadruple therapy meant: Sandimmun + corticosteroids + azathioprine + antibody induction- ie ATG/ALG/ATGAM/OKT3.

Fujisawa submitted that there could be no question in interpreting these dosage recommendations stated in the Sandimmun SPC either from a clinical or a regulatory point of view. The fact was that if Sandimmun was used with corticosteroids or as a triple therapy, the initial oral dose of Sandimmun used might be lower (for example 3-6mg/kg/day). In all of the above mentioned studies doses of Sandimmun were in fact used within the doses stated in the Sandimmun SPC. Based on this fact alone, Fujisawa strongly disputed that there was any breach of Clause 7.2

Fujisawa gave a resumé of each study.

Pichlmayr *et al*. The European Multi-centre Liver Study.

This publication reported on the three year follow-up data of the European liver study and did not provide details of the study medication referring the reader instead to an earlier publication of the same study which described the study medication in full. This was a common practice adopted by publications which reported on the long-term follow-up results, whereby results of the same study had already been published at different time points (ie 6 months, 1 year, 2 years, etc). In such publications, the study design, patient selection, study medication, efficacy and safety evaluation, etc was reported in the earlier publications and the subsequent publications only made reference to them to avoid repetition.

Brief details of the dose regimen were as follows:

- This study was undertaken in four European countries and in eight transplant centres.
- Randomised, open-label multi-centre study.
- Sandimmun's initial daily doses were: 1-6mg/kg given as iv and as oral dose at 8-15mg/kg + azathioprine (1-3mg/kg) + corticosteroids – ATG antibody given at three centres.

The study this used a triple regimen therapy in five centres and a quadruple therapy in three centres. Both the oral and iv administration of Sandimmun was therefore in line with its SPC recommendations, which stated that lower (3-6mg/kg/day) initial doses (rather than 10-15mg/kg/day) could be used if Sandimmun was used with azathioprine, corticosteroids or antibody.

Weisner *et al*. The US Multi-centre Liver Study.

This publication reported on the 5 years follow-up data of the US liver study and although it gave brief details of the study medication, etc full details were published in an earlier publication. Brief details were as follows:

- Study undertaken in the US in twelve transplant centres.
- Randomised, open-label multi-centre study.
- At ten centres Sandimmun given initially as iv (2mg/kg/day) + iv azathioprine (2mg/kg/day) both given pre-operatively + oral Sandimmun at doses to maintain blood levels of 250-400ng/mL + corticosteroids.
- At one centre Sandimmun given initially (4mg/kg/day) pre-operatively for 1-2 days followed by oral Sandimmun at 10mg/kg/day + corticosteroids.
- At one centre azathioprine given pre-operatively (2mg/kg/day as iv or oral) + ATG + corticosteroids + oral Sandimmun on day 4 at doses to maintain blood levels of 250-400ng/mL.
- At all twelve centres Sandimmun doses were adjusted to maintain blood levels between 250-400ng/mL.

The publication did not state the dose of Sandimmun in mg/kg/day, but only as blood levels - this being a standard practice in transplantation when administering Sandimmun. Fujisawa was thus not sure why Novartis was making claims that the doses used were below those recommended as this information was absent from the publication. Confidential details of the dosages used in the study

were provided. A full internal report of this study was compiled from the clinical trial database which gave the dosing for Prograf and Sandimmun from day 0 to day 330. This report showed that the doses of Prograf and Sandimmun were wide ranging (as in all transplantation studies for the reasons outlined above) and were well within the range specified in the Sandimmun SPC.

As could be seen from the above information, Sandimmun was given as triple therapy. In addition Sandimmun was given pre-operatively. The Sandimmun dosage regimen was therefore well in line with its SPC recommendations. Fujisawa considered that based on this alone, this satisfied the concerns expressed by Novartis.

Pirsch *et al*. The US Multi-centre Kidney Study.

This publication reported on the 12-month data for the US kidney study. Details of the study and design and dosing regimen were as follows:

- Study undertaken in the US in 19 transplant centres.
- Randomised, open-label multi-centre study.
- Patients randomised to Sandimmun or Prograf after establishing renal function.
- Initial oral Sandimmun given at 10mg/kg/day and the target blood levels were 150-300ng/mL for the first 3 months and 100-300ng/mL thereafter. Dosing of Sandimmun was adjusted based on blood levels. All patients also received corticosteroids + azathioprine + antibody (OKT3 or ATGAM).
- Initial Prograf was given at 0.2mg/kg/day and the target blood levels were 10-25ng/mL for the first 3 months and 5-15ng/mL thereafter. The dose of Prograf was adjusted based on blood levels. All patients also received corticosteroids + azathioprine + antibody (OKT3 or ATGAM).

Thus, the dosage regimen used for Sandimmun in this study was quadruple therapy and therefore was in line with its SPC recommendations. In addition, the initial dose of 10mg/kg/day of Sandimmun was in line with its SPC recommendations if it was not used as part of multi-drug therapy. Fujisawa also noted that as antibody induction therapy was employed, there was no need to give either Prograf or Sandimmun pre-operatively as the antibody provided protection against rejection for several days. In addition, the medicines were administered once the patient's renal function was established.

Mayer *et al*. The European Kidney Study.

This publication reported on the 12 months results of the European Kidney study. Details of study design and dosing regimen were as follows:

- Study undertaken in seven European countries and fifteen transplant centres
- Randomised, open-label multi-centre study
- Initial dose of Sandimmun was 8mg/kg/day and the dose was adjusted to achieve blood levels of 100-300ng/mL during the first 3 months and 100-150ng/mL thereafter. In addition, all patients received corticosteroids and azathioprine.
- Initial dose of Prograf was 0.3mg/kg and the dose adjusted to achieve blood levels of 10-20ng/mL during the first 3 months and 5-15ng/mL thereafter. In addition, all patients received corticosteroids and azathioprine.

As could be seen, this study also employed a triple therapy regimen and therefore the doses of Sandimmun used were in line with its SPC recommendations. Fujisawa provided confidential details of the dose used which showed that the actual doses of Prograf and Sandimmun were wide ranging (as in all transplantation studies for the reasons outlined above).

Fujisawa stated that the doses of Sandimmun employed in this study were also well within the SPC recommendation, even if it was not used as part of multi-drug therapy.

In summary Fujisawa stated that it was well accepted in the area of transplantation that the initial oral dosing of Prograf or Sandimmun were only recommendations and were intended to act as a guideline. The doses of these agents were then adjusted based on clinical judgement and by measuring blood levels of each. It was also common knowledge that most centres (currently and at the time of these trials) used triple therapy regimen of cyclosporin, azathioprine and corticosteroids to provide immunosuppression without administering each agent at toxic doses.

In conclusion, it could be seen from the information provided above that the studies cited to support the comparative efficacy claims did not use dosage regimens of Sandimmun outside its licensed regimes. Fujisawa was confident that healthcare professionals involved in transplantation would readily interpret its statements in the way they were intended and would find the interpretation suggested by Novartis too far removed from clinical practice. The comparative efficacy statements made in the advertisement formed an accurate, balanced, fair and objective comparison of Prograf and Sandimmun and therefore Fujisawa disputed that there was any breach of Clause 7.2.

PANEL RULING

The Panel noted that the advertisement related to immunosuppression in kidney and liver transplantation. Transplantation was a complex therapy area. Clinicians using the various medicines would be experts in their field. Clinicians might use doses of products outside the licensed recommendations. The Panel noted Fujisawa's submission that, while in initial trials cyclosporin was used as a single agent, today it was usually administered in conjunction with other immunosuppressants. Combination therapy meant that low doses of cyclosporin could be used thus reducing the risk of renal toxicity.

The introductory paragraph of the advertisement at issue compared Prograf with the original formulation of cyclosporin.

The Panel noted that the references cited in support of the comparative efficacy claims for Prograf and the

original formulation of cyclosporin all used cyclosporin as part of triple or quadruple therapy. The Sandimmun SPC gave details of the doses to be administered when the product was to be used as a single agent ie oral treatment should be initiated at 10 to 15mg/kg/day 4 to 12 hours before transplantation continuing for one to two weeks post operatively reducing gradually to a maintenance dose of 2 to 6mg/kg/day. These were the doses cited by Novartis in its complaint. With regard to combination therapy, however, the SPC stated that lower doses could be used and gave, as an example of this, 3 to 6mg/kg/day initially. In the Panel's view, such a dose range, given as an example, was for guidance only and not to be regarded as definitive. The dosage should be adjusted according to cyclosporin blood levels or to serum creatinine and urea levels. The Panel noted that there would be inter- and intra-patient variation in the pharmacokinetics and pharmacodynamics of cyclosporin and that therapy could be tailored by careful assessment of each patient.

The Panel also noted that the iv dose for patients unable to take oral therapy was one third of the recommended oral dose. Patients should be transferred to oral therapy as soon as the given circumstances allowed.

The Panel noted that in Case AUTH/513/2/97 Fujisawa had submitted that although the cyclosporin dosage might not mirror the SPC dosage, the studies did reflect the use of the product in major transplant centres in the UK. The Panel ruled that the dose of Sandimmun used in the cited studies was less than the licensed dose which was unfair and a breach of the Code was ruled.

The Panel considered that the case now before it was different to the previous case (Case AUTH/513/2/970) as Fujisawa had not included in its submission that the dosage regimens in the Sandimmun SPC were recommendations and were not prescriptive. This particular issue had thus not been considered.

Turning to the case before it, the Panel considered that, on balance, the studies cited did not represent an unfair comparison of Prograf and Sandimmun. According to current clinical practice cyclosporin was likely to be used as part of triple or quadruple therapy where doses could be kept low to avoid toxicity. The wording of the SPC was such that the dose range stated for such therapy was not prescriptive and treatment should be tailored to meet individual needs. No breach of Clause 7.2 was ruled.

APPEAL BY NOVARTIS

Novartis stated that the Panel had ruled no breach on the basis of the arguments provided by Fujisawa and the complexity of the transplant therapeutic area. It did not consider that this was an acceptable conclusion.

The advertisement in question appeared in The Lancet, a prestigious journal with a wide readership, and therefore it could not be assumed to have been directed only to specialists familiar with optimal dosing regiments in transplantation. The overwhelming promotional message of the advertisement to non-specialists, therefore, was that tacrolimus had demonstrated superior efficacy to cyclosporin. Novartis continued to argue that this claim was misleading in that the references used to substantiate it did not present a fair comparison between the products.

Cyclosporin as a molecule had been licensed in the UK since 1983. Therefore there now existed a considerable body and wealth of data on the medicine both from pre-registration trials and subsequently post-marketing studies. This wealth of data was reflected in the dosing regimens cited in the SPC for the product. Unlike the SPC for Prograf, there was no statement in the Sandimmun SPC which indicated that the dosage recommendations provided were intended to act as guidelines only, which might simply reflect the larger volume of experience with Sandimmun. Similarly, any dosage modifications required in relation to drug interactions or side effects would still be carried out in accordance with the approved dosage schedules provided in the SPC for the product.

It should be noted that whilst the Prograf SPC did make provision for dosages to be 'guidelines', dose ranges were provided, and therefore it must be assumed that within these ranges the drug had been demonstrated, to the satisfaction of the licensing authorities, to be both safe and effective. Doses outside of these ranges would not be considered acceptable within the terms of the licence, as was the case for any product.

Prograf had been licensed in the UK since 1994 and it was of note that all of the publications cited comparing Sandimmun to tacrolimus referred to studies which were recruiting well before marketing authorisation for the product was granted in the UK, some as early as 1990. It was certainly the case that the doses of tacrolimus used in both the cited liver transplant studies were considerably higher than those subsequently licensed, whilst in the renal studies the dose of the comparator, Sandimmun, was given outside the already accepted licensed dosing schedule for the product.

Novartis was grateful to Fujisawa for its synopsis of the four cited studies in question and for providing additional published details on these studies which had enabled Novartis to review in more detail the doses of tacrolimus and cyclosporin used. Novartis noted that Fujisawa's response had focused on the dosage regiments for Sandimmun and, in particular, for the two liver studies (Pichlmayer and Weisner) the doses of tacrolimus had not been referred to. Fujisawa had, however, provided the dose of tacrolimus in the two renal studies. Novartis, therefore, drew the Appeal Board's attention to the absent data in Fujisawa's response, namely the dose of tacrolimus used in the two liver studies which were as follows.

1 Pichlmayer R *et al* Transplant Proc, 1997

Initial iv dose of 0.075mg/kg bd – 0.15mg/kg/day x 3 days reduced to 0.06mg/kg/day later in the course of the study.

Initial oral dose following iv, 0.3mg/kg/day.

However, it would be noted that the Prograf SPC stated that '… intravenous tacrolimus therapy should

be initiated … at 0.01 to 0.05 mg/kg [per 24 hours] for liver transplants …' and 'oral tacrolimus should commence at 0.10 - 0.20 mg/kg/day for liver transplantation'.

Thus in this study the iv dose employed was initially three times the maximum dose subsequently licensed for the product, and even after later reduction remained higher than the licensed dose throughout the course of the trial. In addition, the initial oral dose exceeded by 1.5 times the maximum licensed dose.

It was reasonable to assume that these higher than licensed doses would have affected the results in favour of tacrolimus. By quoting this study in a promotional piece in support of a comparative efficacy claim for tacrolimus, Fujisawa had both promoted outside of its product licence and provided a damaging and misleading comparison for cyclosporin in breach of Clauses 3.2 and 7.2.

2 Weisner RH. Transplantation 1998

Initial iv dose 0.15mg/kg/day in 48 of 263 patients on tacrolimus, then 0.1mg/kg/day in the remainder. Initial oral dose 0.3mg/kg/day.

As in the previous study referred to, these doses of both iv and oral tacrolimus were considerably higher than the maximum licensed doses referred to in the Prograf SPC and therefore this represented a further breach of Clause 3.2.

Evaluating the advertisement in question as a whole, Novartis continued to have concerns that the efficacy of Sandimmun had been compromised through the adoption of a dosing schedule outside of the licence, in particular the omission of a pre-transplant dose. Novartis' concern, therefore, remained that the use of all four of these studies in the setting of a comparative efficacy claim was misleading and in breach of Clause 7.2.

In addition, Novartis referred the Appeal Board to Case AUTH/839/2/99 which involved the promotion of navelbine for advanced breast cancer. This represented another complicated and highly specialised area in which oncologists were very familiar with individual factors affecting suitability for treatment. In this case, several breaches of Clause 3.2 were identified as studies were cited in which some patients had not received prior anthracycline therapy Whilst clearly not identical, the precedent had been set by this case and one recently involving Novartis' own product Lescol, Case AUTH/988/3/00, that studies including patients who did not fit the licensed dosing schedule for a product were not suitable for use in support of comparative claims.

RESPONSE FROM FUJISAWA

Fujisawa was somewhat surprised as to the grounds on which Novartis had based its appeal. Fujisawa was of the opinion that the arguments which Novartis put forward now had very little relevance to the original complaint.

The original complaint made by Novartis alleged that the advertisement was in breach of Clause 7.2 of the Code. The concern expressed by Novartis was that the comparative efficacy claims were being made citing studies (Pirsch *et al* 1997; Pichlmayr *et al* 1997; Weisner *et al* 1998 and Mayer *et al* 1997) which used doses and dosage regimens of cyclosporin outside of the licensed recommendations for Sandimmun. Novartis had claimed that these doses of Sandimmun were lower than the SPC recommended doses whilst one of the studies (Mayer *et al* 1997) used maximum recommended dose of Prograf, and on this basis this was an unfair comparison and thus alleged a breach of Clause 7.2 of the Code.

The appeal by Novartis no longer cited that the doses and dosage regimens of Sandimmun were outside of the licensed recommendations but, on the contrary, made new allegations focusing on the use of Prograf outside its licensed recommended doses and alleged a new breach of Clause 3.2. It would appear that in doing so, Novartis had tacit acceptance that the doses and dosage regimens of Sandimmun were not outside of the licensed recommendations. This might be an attempt to deliberately mix the new allegations with the original ones in the hope of causing confusion to a matter that had already been clarified and ruled upon by the Panel.

As the original complaint did not allege breaches of issues relating to Clause 3.2, it would not therefore be subject to an appeal. In view of this Fujisawa would respond with reference to Clause 7.2 only. In doing so, it would relate its response to those elements in the appeal which, in Fujisawa's understanding, related to the original complaint only.

Novartis' appeal started by making bold assumptions that the Panel's ruling was based mainly on the arguments relating to the 'complexity of the therapeutic area'. This was in sharp contrast to the response made by Fujisawa and the Panel's ruling. The fact was that the Sandimmun SPC stated clearly in the 'Dosage and administration' section:

'When Sandimmun is given with other immunosuppressants (eg with corticosteroids or as part of a triple or quadruple drug therapy) lower doses (eg 3-6mg/kg/day orally initially) may be used'.

There could be no question in interpreting these dosage recommendations stated in the Sandimmun SPC either from a regulatory or a clinical point of view. The fact was that if Sandimmun was used with corticosteroids or as part of a triple or quadruple therapy, the initial oral dose of Sandimmun used might be lower (for example 3-6mg/kg/day). The fact was that in all of the studies in question, Sandimmun was used as part of a triple or quadruple drug therapy. Therefore, doses of Sandimmun were in fact used within the doses stated in the Sandimmun SPC for the UK. Based on this fact, Fujisawa strongly disputed that there could be a breach of Clause 7.2. Fujisawa's original response provided a comprehensive and detailed analysis of the dosing regimen of Sandimmun for each study and all these were discussed in relation to the recommendations made in the Sandimmun SPC.

In its ruling, the Panel had clearly noted that all of the studies in question had used Sandimmun with corticosteroids and as triple or quadruple therapy and

were in line with the Sandimmun SPC. This fact was made clear in the Panel's ruling. Therefore based on this, together with the knowledge that the area of immunosuppression in transplantation was a complex area and that dosing was individualised according to clinically important factors and on monitoring of blood levels, the Panel found no breach of Clause 7.2 of the Code.

Fujisawa found it very unusual that Novartis was suggesting that its medicine was only being used in line with its SPC as per its claims. However, in reality the medicine was used in the clinical setting as outlined in the Panel's ruling which stated: 'According to current clinical practice cyclosporin was likely to be used as part of a triple or quadruple therapy where doses could be kept low to avoid toxicity. The wording of the SPC was such that the dose range stated for such therapy was not prescriptive and treatment should be tailored to meet individual needs.' and 'The SPC also stated that dosage should be adjusted according to cyclosporin blood levels or to serum creatinine and urea levels. The Panel noted that there would be inter- and intra-patient variation in the pharmacokinetics and pharmacodynamics of cyclosporin and that therapy could be tailored by careful assessment of each patient.'

This suggestion made by Novartis was clearly designed to mislead, since its very own studies did not use its medicine in the setting it was claiming. In these Novartis sponsored studies, the protocols employed for Sandimmun were very similar to the Fujisawa studies under consideration.

In the appeal, the following arguments were put forward.

'Cyclosporin as a molecule has been licensed in the UK since 1983, therefore there now exists a considerable body and wealth of data on the drug both from pre-registration trials and subsequently post-marketing studies. This wealth of data is reflected in the dosing regimens cited in the SPC for the product. Unlike the SPC for Prograf, there is no statement in the Sandimmun SPC which indicates that the dosage recommendations provided are intended to act as guidelines only, which may simply reflect the larger volume of experience with Sandimmun. Similarly, any dosage modifications required in relation to drug interactions or side effects would still be carried out in accordance with the approved dosage schedules provided in the SPC for the product'.

Fujisawa's original submission and its response above had dealt with this issue and the Panel had already ruled no breach of Clause 7.2 on this.

'It should be noted that whilst the Prograf SPC … doses of tacrolimus used in both the cited liver studies were considerably higher than those subsequently licensed.'

The original complaint did not allege a breach of Clause 3.2 and thus it could not therefore be subject to an appeal and no response was required from Fujisawa. Nevertheless, it wished to point out that the recommended doses in the Prograf SPC were based on the actual doses and dosage regimens used and the data generated in the cited studies.

'… Sandimmun, was given outside the already accepted dosing schedule for the product.'

Fujisawa's original submission and its response above had dealt with this and the Panel had already ruled no breach on this.

Novartis also stated 'We are grateful to Fujisawa for their synopsis of the four cited studies and for providing additional published details on these studies which has enabled us to review in more detail the doses of tacrolimus and cyclosporin used.' This implied that Fujisawa had given Novartis new information to base its appeal upon. This was factually incorrect since there was no additional information provided on the four studies in question. The information on these four studies (Pirsch *et al* 1997, Pichlmayr *et al* 1997, Weisner *et al* 1998 and Mayer *et al* 1997) had already been published in the respective journals and had always been available in the public domain since 1997. Therefore, there was no additional information provided other than what was already published in these studies.

Again, the original complaint did not allege a breach of Clause 3.2 and thus it could not therefore be subject to an appeal and no response was required from Fujisawa. In addition, it was worth pointing out that Fujisawa's original response was only concerned with the dosage regimens of Sandimmun and not that of Prograf (as per the original complaint) and this fact was clearly stated in Fujisawa's response letter.

'Evaluating the advertisement in question … efficacy claim is misleading and in breach of Clause 7.2.'

Fujisawa's original submission and its response above had already dealt with this and argued that the studies cited did not represent an unfair or unbalanced comparison of Prograf and Sandimmun. The Panel had already ruled no breach on this.

Reference to Case AUTH/839/2/99 where several breaches of Clause 3.2 were identified and one recently involving Novartis' own product Lescol, Case AUTH/988/3/00.

Having noted the contents of these two other cases and the circumstances which led to these complaints, Clause 3.2 was breached, Fujisawa did not consider that these cases had any relevance whatsoever to the case under consideration.

Fujisawa was certain that the Appeal Board would find the Panel's decision of no breach of Clause 7.2 correct and agree that The Lancet advertisement formed a fair and balanced comparison of Prograf and Sandimmun. Fujisawa also hoped the Appeal Board would comment on the unacceptable attempt by Novartis to introduce a new clause into its appeal.

FURTHER COMMENTS FROM NOVARTIS

Novartis stated that in its original complaint it had alleged a breach of Clause 7.2 on the basis that inappropriate doses of tacrolimus and cyclosporin were compared leading to misleading claims being made for Prograf. Novartis' initial assertion still

stood, and the facts remained that the studies cited (Mayer *et al* 1997, Pirsch *et al* 1997, Pichlmayr *et al* 1997 and Weisner 1998) all used lower than the licensed doses of Sandimmun (the cyclosporin formulation used in these studies). The two renal studies (Mayer and Pirsch) did not use a pre-transplant dose of Sandimmun, and the two liver studies (Pichlmayr and Weisner) used lower than the initial recommended doses of Sandimmun. It should be noted that the detail of the two liver studies was derived from earlier references.

In addition to using a lower than licensed dose of Sandimmun, the two liver studies also used a higher than licensed dose of tacrolimus as demonstrated in Novartis' appeal.

Thus the comparison of tacrolimus and cyclosporin did not compare like with like and was therefore not fair, accurate or balanced, and was in breach of Clause 7.2.

Novartis reminded the Appeal Board that the use of the Pirsch (renal) and Pichlmayr and Weisner (liver) studies to support comparative efficacy claims had already been the subject of Case AUTH/513/2/97 when Fujisawa was found in breach of Clause 7.2. In this case 'The Panel considered, however, that it was unfair to compare Prograf with Sandimmun at doses below the licensed dose. A breach of the Code was ruled.'

With reference to the citation of the two liver studies where doses of tacrolimus outside the licence were used to promote Prograf, Novartis believed this to be a clear breach of Clause 3.2. Novartis had already been informed by the Director of the Authority that this should be the subject of a separate complaint. Novartis acknowledged this and had made a separate complaint.

Novartis further confirmed that the original formulation of cyclosporin, Sandimmun did have a product licence but was made available on a named patient basis only.

APPEAL BOARD RULING

The Appeal Board noted that transplantation was a highly specialised and complex area. Clinicians using the various medicines would be experts in the field. The Appeal Board noted the submission from Fujisawa that cyclosporin was usually administered with other immunosuppressants. The Appeal Board noted the section of the Sandimmun SPC headed 'Dosage and administration' which stated that 'When Sandimmun is given with other immunosuppressants (eg corticosteroids or as part of a triple or quadruple drug therapy) lower doses (eg 3-6mg/kg/day orally initially) may be used'.

The Appeal Board noted that various pharmacokinetic and pharmacodynamic factors needed to be taken into account when administering Sandimmun or Prograf which would influence the dosage regimen of either of these medicines. Continuous monitoring and dose adjustment was required post transplant with dosing tailored to meet individual needs. Transplant specialists would be familiar with these clinically important factors.

The Appeal Board noted the views expressed by the Fujisawa representatives regarding the studies. Prograf was compared with the best Sandimmun based regimen. The representatives stated that the use of pre-transplant doses of Sandimmun varied. Most transplant centres in Europe did not use pre-transplant doses. Steroid loading doses were used. US centres did use pre-transplant doses. A comment was made that the population mix was different in the US to Europe. Clinical practice was to base immunosuppressive therapy on monitoring of blood levels and the overall clinical condition of the patient. Inter-patient variability meant that dosing needed to be individualised on a patient by patient basis.

The Appeal Board noted that the doses of Sandimmun used in the studies were not outside the Sandimmun SPC. The product was administered with corticosteroids as part of triple or quadruple therapy. The Appeal Board was satisfied with the response from Fujisawa with regard to current clinical practice and the use of pre-transplant dose. The best Sandimmun based regimen had been used in the studies. The Appeal Board noted that the studies had been used for registering Prograf in Europe and the US. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.2 of the Code. The appeal was unsuccessful.

Complaint received **1 June 2000**

Case completed **6 September 2000**

CASE AUTH/1031/6/00

PHARMACIST/DIRECTOR v SCHWARZ PHARMA

Breach of undertaking

A prescribing support pharmacist, who had been the complainant in Case AUTH/967/1/00, complained that Schwarz Pharma was continuing to take account of pharmacist dispensing fees and container allowances in its claim that it was less expensive to prescribe Tylex than its generic components separately. It had been the Panel's view in Case AUTH/967/1/00 that it was too simplistic to include dispensing fees in the calculations to support a claim for a 12% cost advantage for Tylex compared to individually prescribed generic paracetamol and generic codeine. The effect of the dispensing fee and container allowance on NHS costs was more complicated than the impression given. A breach of the Code had been ruled. The complainant drew attention to a Tylex advertisement which had been published in Guidelines in Practice, May 2000. The advertisement stated 'And unlike Tylex, individually prescribed paracetamol 500mg tablets and codeine 30mg tablets attract two pharmacist dispensing fees and two container allowances.'

As the complaint involved a possible breach of undertaking, the matter was taken up as a complaint by the Director of the Authority as the Authority itself was responsible for ensuring compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

The Panel noted that the claim now at issue was 'And, unlike Tylex, individually prescribed paracetamol 500mg tablets and codeine 30mg tablets attract two pharmacist dispensing fees and two container allowances'. It was then stated that prescribing Tylex was actually less expensive than prescribing the generic components separately. The Panel considered that although different to the claim in Case AUTH/967/1/00, the claim now at issue was similarly misleading and sufficiently similar for it to be caught by the undertaking given in the previous case. Schwarz had thus failed to comply with its undertaking. A breach of the Code was ruled as acknowledged by Schwarz.

The Panel noted that the advertisement had been placed by a product manager only weeks after Schwarz had given the undertaking in the previous case. 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 important for the reputation of the industry that companies complied with undertakings. The Panel noted that although Schwarz had taken steps to ensure compliance with the undertaking given in Case AUTH/967/1/00 these had not been wholly adequate. A product manager had been able to use an advertisement which should have been withdrawn. The Panel considered that the continued use of a claim previously ruled in breach of the Code brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. The Panel noted that Schwarz had since introduced procedures to ensure that such an error could not occur again. The Panel noted that the Constitution and Procedure required it to report a company to the Appeal Board if it failed to comply with procedures or if its conduct in relation to the Code warranted consideration by the Appeal Board.

Failure to comply with an undertaking was a serious matter. However, the Panel decided that the circumstances did not warrant reporting Schwarz to the Appeal Board.

COMPLAINT

A prescribing support pharmacist, the complainant in Case AUTH/967/1/00, complained that Schwarz Pharma Limited was continuing to take account of pharmacist dispensing fees and container allowances in its claim that it was less expensive to prescribe Tylex than its generic components separately. It had been the Panel's view in Case AUTH/967/1/00 that it was too simplistic to include dispensing fees in the calculations to support a claim for a 12% cost advantage for Tylex compared to individually prescribed generic paracetamol and generic codeine. The effect of the dispensing fee and container allowance on NHS costs was more complicated than the impression given. A breach of the Code had been ruled.

The complainant drew attention to a Tylex advertisement which had been published in Guidelines in Practice, May 2000. The advertisement stated 'And unlike Tylex, individually prescribed paracetamol 500mg tablets and codeine 30mg tablets attract two pharmacist dispensing fees and two container allowances.' The complainant had understood that Schwarz had withdrawn the advertisement at issue in Case AUTH/967/1/00 and would no longer include pharmacist dispensing fees in its advertisements as the Panel had ruled that this was misleading and in breach of Clause 7.2 of the Code.

* * * * *

As the complaint involved a possible breach of undertaking, the matter was taken up as a complaint by the Director of the Authority as the Authority itself was responsible for ensuring compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

RESPONSE

Schwarz Pharma agreed that the advertisement was in contravention of the undertaking given in Case AUTH/967/1/00; with this in mind the advertisement was in breach of Clauses 7.2 and 21 of the Code.

Schwarz explained that following its acceptance of the rulings of a breach of the Code in the previous case the 'priceless' campaign was withdrawn. It was replaced by a campaign known as 'priceless evidence' which ran until April this year in various journals. Unfortunately in May the product manager (who had

subsequently left the company) erroneously instructed that the 'priceless' advertisements be run rather than the 'priceless evidence' advertisements. This error had now been rectified and the 'priceless' campaign had been withdrawn once again.

Schwarz submitted that bearing in mind the above points and the fact that this breach had arisen out of unfortunate human error rather than intent, it proposed that no breach of Clause 2 should be ruled. The company added that since this matter was brought to its attention it had instigated procedures to ensure that such errors could not occur in the future.

PANEL RULING

The Panel noted that the complainant had understood that as a consequence of the ruling in Case AUTH/967/1/00, Schwarz could no longer refer to pharmacists' fees in its advertisements. This was not so. It was the linking of such fees to the NHS cost of Tylex that was prohibited not the discussion of such fees *per se*.

The Panel noted that in Case AUTH/967/1/00 pharmacists' dispensing fees and container allowances had been used in a calculation to claim that Tylex capsules were 12% lower in cost than the equivalent, individually prescribed generic paracetamol and generic codeine tablets. The Panel had considered that as the effects of dispensing fees and container allowances on NHS costs was more complicated than the impression given the material was misleading and a breach of the Code was ruled.

The Panel noted that the claim now at issue was 'And, unlike Tylex, individually prescribed paracetamol 500mg tablets and codeine 30mg tablets attract two pharmacist dispensing fees and two container allowances.' It was then stated that prescribing Tylex was less expensive than prescribing the generic components separately. The Panel considered that, although different to the claim in Case AUTH/967/1/00, the claim now at issue was similarly misleading and sufficiently similar for it to be caught by the undertaking given in the previous case. Schwarz had thus failed to comply with its undertaking. A breach of Clause 21 was ruled as acknowledged by Schwarz. The Panel considered that its ruling of a breach of Clause 21 covered the allegation of a breach of Clause 7.2 of the Code.

The Panel noted that the advertisement had been placed by a product manager only weeks after Schwarz had given the undertaking in the previous case. 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 important for the reputation of the industry that companies complied with undertakings. The Panel noted that although Schwarz had taken steps to ensure compliance with the undertaking given in Case AUTH/967/1/00 these had not been wholly adequate. A product manager had been able to use an advertisement which should have been withdrawn. The Panel considered that the continued use of a claim previously ruled in breach of the Code brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. The Panel noted that Schwarz had since introduced procedures to ensure that such as error could not occur again.

The Panel noted that the Constitution and Procedure required it to report a company to the Appeal Board if it failed to comply with procedures or if its conduct in relation to the Code warranted consideration by the Appeal Board (Paragraphs 8.1 and 8.2). Failure to comply with an undertaking was a serious matter. However, the Panel decided that the circumstances did not warrant reporting Schwarz to the Appeal Board.

Complaint received **1 June 2000**

Case completed **21 July 2000**

CASE AUTH/1032/6/00

HOSPITAL PHARMACIST v ASTRAZENECA

Presentation on Accolate

A pharmacist in a hospital cardiac intensive care unit complained about a presentation which had been made by an AstraZeneca representative in relation to Accolate (zafirlukast). It was alleged that there had been selective presentation of data about Accolate and montelukast (Merck Sharp & Dohme's product Singulair), drawing unfair conclusions.

The complainant said that the representative presented an acetate demonstrating that zafirlukast reduced exacerbations requiring the need for oral steroids by 48%, statistically significantly more so than placebo, and then presented a summary of montelukast results which demonstrated that there was no significant difference between montelukast and placebo with regard to requirement for oral steroids. The representative then stated that as zafirlukast was more effective than montelukast, and if montelukast therapy had failed, it was still worth using zafirlukast. The complainant alleged that a glance at the relevant data did not bear out the implication of these claims. The data was an unpublished meta-analysis with a completely inadequate description of methodology, references and results. It stated that zafirlukast halved the risk of requirement of oral steroids. However the difference in absolute terms was a reduction from approximately 6% to 3%. Therefore the number to treat (NNT) to achieve this was 33 (100/3). The complainant stated that the montelukast data results presented were correct. However what was not stated was that 'Patients treated with montelukast experienced fewer days with asthma exacerbations (a decrease of 31%) and more asthma control days (an increase of 37%) than patients receiving placebo (p<0.001). The absolute differences were ~15% v 10% and ~35% v 30% respectively. Both of these results suggested a NNT of ~20. Thus from the results used in the presentation the NNT to achieve an objective response was actually higher for zafirlukast than for montelukast. In the complainant's view the presentation was misleading in suggesting that montelukast was less effective and when questioned the representative could produce no data to justify the claim that zafirlukast might work where montelukast failed.

The Panel noted that the relevant representatives' briefing material was arranged such that both slides appeared on one page of the briefing notes. Separate paragraphs described the two studies. The third paragraph stated that exacerbation reduction was one of the key aims outlined in the British Thoracic Society (BTS) Guidelines. The Panel noted that in the presentation the zafirlukast slide immediately preceded the montelukast slide. Each slide featured an identical main heading and similar design. The Panel considered that the positioning and format of the slides invited a direct comparison between the data presented. The use of non-comparative data might be acceptable in certain circumstances; relevant factors would be the therapy area, the intended audience, how the data was presented and the conclusions drawn.

The slides at issue were both headed 'Separate published data showing exacerbation reductions as assessed by the requirement for short courses of oral steroids' and each included a bar chart. The Accolate data was referenced to Hassall *et al* (1998) and to data on file. The bar chart showed that Accolate had demonstrated a statistically significant reduction in exacerbations by 47% (p=0.01). The montelukast data was from Reiss *et al* (1998). It was stated that there was no significant difference in percentage of patients with exacerbations between montelukast and placebo. The bar chart showed that the 28% reduction in exacerbations was not statistically significant. The Panel noted that an abstract of the data had been published. The pooled data were used to assess the relative risk of asthma exacerbations using three definitions: worsening of asthma leading to withdrawal from the study, requirement for additional anti asthma therapy (excluding increased short acting ß$_2$ agonist use) and requirement for oral corticosteroid therapy. The trials used were in steroid-naïve patients with mild to moderately severe asthma. None of the patients were using oral or inhaled corticosteroids or long-acting ß$_2$ agonists at entry to the trial. The study by Reiss *et al* 1998 was carried out on patients with chronic stable asthma. All patients used short acting inhaled ß-agonists as needed and a percentage of patients not exceeding 25% were allowed concomitant inhaled steroids at a constant dosage beginning at least four weeks before the pre-study visit. Forced expiratory flow (FEV$_1$) and daytime asthma symptom score were prespecified as primary end points. There were a number of other prespecified end points including episodes of worsening asthma (percentage of days with asthma exacerbations), use of rescue oral corticosteroids (percentage of patients) and discontinuation because of worsening asthma (determined by whether additional asthma medications were required). Patients treated with montelukast experienced fewer days with asthma exacerbations (a decrease of 31%) and more asthma control days (an increase of 37%) than patients receiving placebo (p<0.001). Fewer patients (a decrease of 28%) treated with montelukast required oral corticosteroid rescues (6.9% compared with 9.6% for placebo, p = 0.20) and fewer patients (a decrease of 59.5%) discontinued therapy because of worsening asthma (1.5% compared with 3.7% for placebo, p = 0.07). The Panel noted that a number of the parameters investigated in this study showed statistically significant advantages for montelukast compared to placebo.

The Panel queried why AstraZeneca had used data for exacerbation reductions based on the requirement for short courses of oral steroids. These only related to one parameter of asthma control. The Panel considered that it was very difficult to compare fairly the results of one study with another separate study. The Panel queried the effect of the fact that in the Reiss study up to 25% of patients were allowed concomitant inhaled steroids at a constant dosage beginning at least four weeks

before the pre-study visit. There were different patient populations. The Panel considered that the comparison was unfair. A breach of the Code was ruled.

COMPLAINT

A hospital ICU/cardiac directorate pharmacist complained about a presentation made by a medical representative of AstraZeneca UK Limited. The representative was promoting Accolate (zafirlukast). The complaint concerned the alleged selective presentation of data about Accolate and montelukast (Merck Sharp and Dohme Limited's product Singulair) drawing unfair conclusions.

The complainant stated that the representative presented an acetate demonstrating that zafirlukast reduced exacerbations requiring the need for oral steroids by 48%, statistically significantly more so than placebo. The representative then presented a summary of montelukast results which demonstrated that there was no significant difference between montelukast and placebo with regard to requirement for oral steroids. The representative then stated that as zafirlukast was more effective than montelukast, and if montelukast therapy had failed it was still worth using zafirlukast.

The slides at issue were both headed 'Separate published data showing exacerbation reductions as assessed by the requirement for short courses of oral steroids' and each included a bar chart. The Accolate data was referenced to Hassall *et al* (1998) and to data on file. The bar chart showed that Accolate had demonstrated a statistically significant reduction in exacerbations by 47% (p=0.01). The montelukast data was from Reiss *et al* (1998). It was stated that there was no significant difference in percentage of patients with exacerbations between montelukast and placebo. The bar chart showed that the 28% reduction in exacerbations was not statistically significant.

The complainant alleged that a glance at the relevant data did not bear out the implication of these claims. The data was an unpublished meta-analysis with a completely inadequate description of methodology, references and results. It stated that zafirlukast halved the risk of requirement of oral steroids. However the difference in absolute terms was a reduction from approximately 6% to 3%. Therefore the number to treat (NNT) to achieve this was 33 (100/3).

The complainant stated that the montelukast data results presented were correct, however what was not stated was that 'Patients treated with montelukast experienced fewer days with asthma exacerbations (a decrease of 31%) and more asthma control days (an increase of 37%) than patients receiving placebo (p<0.001). The absolute differences were ~15% v 10% and ~35% v 30% respectively. Both of these results suggested a NNT of ~20.

Thus from the results used in the presentation the NNT to achieve an objective response was actually higher for zafirlukast than for montelukast.

In the complainant's view the presentation was misleading in suggesting that montelukast was less effective and when questioned the representative could produce no data to justify the claim that zafirlukast might work where montelukast failed. The complainant also objected to the increasing trend of presenting unpublished data to slate competitors' medicines. A breach of Clause 7.2 of the Code was alleged which stated that claims must be '…balanced, fair, objective, and reflect the evidence clearly'.

RESPONSE

AstraZeneca stated that its Accolate sales team had been briefed to use a product presentation on acetate in the hospital setting. The company had interviewed the representative concerned about the meeting in question.

The zafirlukast slide depicting reduction in exacerbations showed the results of a meta-analysis by Hassall *et al*. The meta-analysis encompassed data from five 13-week placebo-controlled double-blind clinical trials of zafirlukast 20mg bd in steroid-naïve patients with mild to moderate asthma who were maintained on beta-agonists alone on an as required basis. The purpose of the meta-analysis was to assess the incidence of acute asthma exacerbation in a large population of patients treated with zafirlukast. Acute asthma exacerbation was defined as an exacerbation requiring withdrawal from the study and/or treatment with acute bursts of oral steroids. In all 972 patients were treated with zafirlukast and the results of the meta-analysis showed that there was a statistically significant reduction in asthma exacerbations requiring oral corticosteroid use (odds ratio 0.53; 95% confidence interval 0.32 to 0.86 p=0.01). A statistically significant reduction in asthma exacerbation as defined by withdrawal from the study was also shown (odds ratio 0.44; 95% confidence interval 0.26-0.76 p=0.003). The company chose to depict the information on oral steroid use in its materials, equally it could have depicted that on withdrawal from the study due to exacerbations. The important point was that a robust and objective measure of asthma exacerbation was used that was accepted as such by clinicians.

AstraZeneca stated that at the time of producing the materials in question, these data had not been formally published, they had been presented at the Annual International Conference of the American Thoracic Society (ATS) in San Francisco in April 1998. As abstract from this congress, together with data on file that provided more detailed information on the study, were referenced on the slide. Subsequent to the production of the slide and briefing materials, the results of the meta-analysis had been published in full in a peer-reviewed journal.

AstraZeneca believed that the data were robust, involved a large number of patients and demonstrated a statistically and clinically meaningful benefit of zafirlukast in terms of a reduction in asthma exacerbations. AstraZeneca pointed out that reduction of asthma exacerbations was an important goal of asthma therapy and this was reflected by use of exacerbations as an outcome measure in clinical trials. In this context, AstraZeneca therefore considered that it was legitimate to present the results

of the meta-analysis to an audience of health professionals, whose interest in it could reasonably be assumed.

One of the complainant's concerns was that the abstract did not adequately support the claim of reduction in exacerbations as made during the presentation. Abstracts were of necessity brief descriptions of study methodology, results and conclusions. Further details of the study in question were available in the form of data on file, at the time that the complaint was initiated (as referenced in the slides). However, AstraZeneca understood that in this instance, the abstract was provided in response to a request from one of the attendees at the meeting itself, who had asked to see information on which the slide was based. The representative did not possess a copy of the data on file, but did have a copy of the abstract in her possession at the time of the meeting which she passed to the enquirer. The company understood that further information was not requested, specifically the data on file. AstraZeneca therefore disagreed with the complainant's view that the data that supported the claim were inadequate. The company accepted that at the meeting in question the full supportive data were not immediately available, however it was not its normal practice to provide such data at meetings, full supporting references were always available via its medical information department. AstraZeneca did not believe that any breach of the Code had thereby occurred since the referenced data on file could have been provided, had they been requested.

AstraZeneca stated that given that zafirlukast and montelukast were currently the only leukotriene antagonists on the market and both had been introduced only comparatively recently, it was unsurprising that no directly comparative clinical data existed. However, it believed it was reasonable to refer to data on both products as it was asked questions by health professionals. Presentation of non-comparative data, provided it was clearly stated as such and was neither unbalanced nor misleading, seemed to be appropriate in the circumstances.

Particular features where data common to both products existed, were those concerning pharmacokinetic parameters and outcome data looking at asthma exacerbations. The company's promotional material therefore summarised relevant information, available in the public domain. Data on exacerbation reduction were purposely presented in two separate acetates and titled as separate studies.

AstraZeneca submitted that this was a reasonable approach, it had made it abundantly clear in all its materials where data had been taken from separate studies. It did not accept that it was misleading the recipients of the information, or seeking to disparage a competitor as alleged by the complainant. The representatives had not been briefed to disparage montelukast and the representative in question assured the company that she had not done so.

AstraZeneca pointed out that the complainant acknowledged that the data presented on montelukast were factually correct. They related to a large randomised, multicentre double blind placebo controlled study in 681 patients with chronic stable asthma. The study protocol allowed a two week wash out period followed by a 12 week active treatment period during which patients were randomised to receive either placebo or montelukast 10mg od. Amongst the prespecified end points were use of rescue oral corticosteroids and discontinuation because of worsening asthma. Thus, the design and patient populations of the studies included in the meta-analysis for zafirlukast, were reasonably similar to those of the montelukast study. To the best of the company's knowledge, this was the only published study on montelukast that utilised oral corticosteroid rescue as an independent outcome measure of exacerbations.

The results of the study showed that in comparison with placebo, fewer patients (a decrease of 28%) treated with montelukast exhibited a requirement for oral corticosteroid rescue (6.9% compared with 9.6%), however the difference did not achieve statistical significance, ($p=0.20$). This information was depicted on the slide. Although not shown in the materials, the study also showed that fewer patients on montelukast discontinued therapy because of worsening asthma, but again the difference was not statistically significant (1.5% compared with 3.7%, $p=0.07$).

In view of the above, AstraZeneca was unable to agree that by presenting factually correct data on the same outcome measure for two products, recognised to be important in the management of asthma, the company had been misleading or unbalanced as alleged. In response to the complainant's assertion that the presentation suggested that montelukast was less effective than zafirkulast, AstraZeneca respectfully pointed out that nowhere in the presentation had it made such a claim. The representative had also assured the company that at no time during her presentation did she state that zafirkulast was superior to montelukast. The representative acknowledged that she drew the audience's attention to the slide that depicted the lack of a statistically significant difference in use of oral steroid rescue, but she used the opportunity only to make the point that the two products were different, with different profiles. She then proceeded to make the suggestion that, on this basis, it should not be assumed that where montelukast had not proved efficacious in a particular patient, then this ruled out the possibility that zafirlukast might be successfully used.

AstraZeneca accepted the complainant's point that there were no specific published clinical data to demonstrate that zafirlukast would work in patients in whom montelukast had failed, however it was not claiming that this was so. The representative's point was that, if it was accepted that the two products were different, it followed from first principles that it might be reasonable to consider using zafirlukast in a patient who had not shown improvement on montelukast. The company was not aware of any data which would suggest that zafirkulast would consistently fail in these circumstances.

The representative had further stated that she also supplied a copy of a recently published study report by Calhoun *et al*, to provide further support for

zafirlukast's role in intervention in the inflammatory process in asthma. She had hoped that this would help to address the concerns of the person who questioned her on the above point.

As discussed above, AstraZeneca stated that it had been careful not to make direct comparisons between zafirlukast and montelukast, which it did not believe would be appropriate. The complainant had however chosen to make a direct comparison on the basis of numbers needed to treat (NNT) to achieve an objective response. It should be noted that the data quoted, unlike the information from the presentation, did not utilise the same measure of objective response. The complainant had compared data on asthma exacerbation using the stringent definition of use of oral corticosteroid rescue for zafirlukast, whilst adopting different outcome measures for montelukast (percentage days asthma exacerbations and percentage days asthma control). These latter outcome measures tended to define comparatively mild asthma exacerbations. Had the complainant calculated NNT on the same outcome measure (use of oral corticosteroid rescue) as used in the presentation, the complainant would have derived a lower NNT for zafirlukast compared to montelukast (33 versus 37, respectively).

AstraZeneca had not presented data on NNTs or briefed its representatives to discuss them. It understood that at the meeting in question, the subject of NNTs was not raised. AstraZeneca was unable to agree that the complainant's retrospective interpretation of the data using NNTs represented a more balanced approach than its own. Whilst it recognised that there were of course different ways of interpreting and presenting data it would suggest that in this instance the use of NNTs had not really added any meaningful information to the debate.

In summary, AstraZeneca did not accept that its presentation was misleading or unbalanced or disparaged montelukast and therefore denied a breach of Clause 7.2 of the Code.

PANEL RULING

The Panel first dealt with the issue of using a reference to data on file in promotional material. It was not unacceptable *per se* to reference claims to data on file. The Code required that any information, claim or comparison must be capable of substantiation and that substantiation must be provided without delay at the request of a health professional (Clauses 7.3 and 7.4). The data supplied to substantiate claims, etc, would be judged on its merits. Companies were not prohibited from using data on file to substantiate claims. Data on file was often used whilst publication of studies, etc, was awaited, as in this case. Following a request for substantiation at a promotional meeting it was acceptable for the company to provide the data after the meeting provided it was supplied without delay. The Panel noted that AstraZeneca had provided a copy of the data on file it would have sent together with the Hassall *et al* abstract to substantiate the claim for Accolate. The data had subsequently been published in a peer reviewed journal.

The Panel noted that the relevant representatives' briefing material was arranged such that both slides appeared on one page of the briefing notes. Separate paragraphs described the two studies. The third paragraph stated that exacerbation reduction was one of the key aims outlined in the British Thoracic Society (BTS) Guidelines.

The Panel noted that in the presentation the zafirlukast slide immediately preceded the montelukast slide. Each slide featured an identical main heading and similar design. The Panel considered that the positioning and format of the slides invited a direct comparison between the data presented.

The Panel considered that the use of non-comparative data might be acceptable in certain circumstances; relevant factors would be the therapy area, the intended audience, how the data was presented and the conclusions drawn.

The Panel noted that the abstract had been published in Thorax 2000. The pooled data were used to assess the relative risk of asthma exacerbations using three definitions: worsening of asthma leading to withdrawal from the study, requirement for additional anti asthma therapy (excluding increased short acting $ß_2$ agonist use) and requirement for oral corticosteroid therapy. The trials used were in steroid-naïve patients with mild to moderately severe asthma. None of the patients were using oral or inhaled corticosteroids or long-acting $ß_2$ agonists at entry to the trial.

The study by Reiss *et al* 1998 was carried out on patients with chronic stable asthma. All patients used short acting inhaled ß-agonists as needed and a percentage of patients not exceeding 25% were allowed concomitant inhaled steroids at a constant dosage beginning at least four weeks before the pre-study visit. Forced expiratory flow (FEV_1), and daytime asthma symptom score were prespecified as primary end points. There were a number of other prespecified end points including episodes of worsening asthma (percentage of days with asthma exacerbations) use of rescue oral corticosteroids (percentage of patients) and discontinuation because of worsening asthma (determined by whether additional asthma medications were required). Patients treated with montelukast experienced fewer days with asthma exacerbations (a decrease of 31%) and more asthma control days (an increase of 37%) than patients receiving placebo ($P<0.001$). Fewer patients (a decrease of 28%) treated with montelukast required oral corticosteroid rescues (6.9% compared with 9.6% for placebo, $p = 0.20$) and fewer patients (a decrease of 59.5%) discontinued therapy because of worsening asthma (1.5% compared with 3.7% for placebo, $p = 0.07$). The Panel noted that a number of the parameters investigated in this study showed statistically significant advantages for montelukast compared to placebo.

The Panel queried why AstraZeneca had used data for exacerbation reductions based on the requirement for short courses of oral steroids. These only related to one parameter of asthma control. The Panel considered that it was very difficult to compare fairly the results of one study with another separate study.

The Panel queried the effect of the fact that in the Reiss study up to 25% of patients were allowed concomitant inhaled steroids at a constant dosage beginning at least four weeks before the pre-study visit. There were different patient populations. The Panel considered that the comparison was unfair. A breach of Clause 7.2 of the Code was ruled.

Complaint received **2 June 2000**

Case completed **10 August 2000**

CASES AUTH/1033/6/00 & AUTH/1039/6/00 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER v ASTRAZENECA and TAKEDA

Amias detail aid

A general practitioner complained about a cost comparison which appeared in an Amias (candesartan) detail aid issued jointly by AstraZeneca and Takeda. Amias was an angiotensin II receptor antagonist (AIIRA). A bar chart headed 'Am I as competitively priced as other leading AII receptor antagonists? Comparative cost of 28 days' therapy' compared the cost of Amias 2-16mg with leading brands of AII receptor antagonists; valsartan 40-160mg, irbesartan 75-300mg, losartan 25-100mg; leading brands of ACE inhibitors, lisinopril 2.5-40mg, enalapril 2.5-40mg, and the leading brand of calcium antagonist, amlodipine 5-10mg. The complainant stated that the bar chart purported to show a cost comparison of Amias against other antihypertensives but included a dose of Amias which was only used in exceptional circumstances and, indeed, was not even available in one month packs. Because this low 2mg dose was included on the bar chart the complainant believed it gave the misleading impression that Amias was better value than some of its competitors. The complainant had written to AstraZeneca several times about this and its responses had left him unsatisfied.

The Panel noted that the left-hand page facing the cost comparison chart was headed 'A suitable choice for a wide range of hypertensive patients'. Four patient profiles were given including an elderly patient and one with some degree of renal impairment. Patients in these two groups might require a reduced dose of Amias. The Amias summary of product characteristics stated that the starting dose was 4mg once daily. The usual maintenance dose was 8mg once daily and the maximum dose was 16mg once daily. An initial dose of 2mg was indicated in elderly patients with reduced renal or hepatic function and in patients with moderate to severe renal impairment or mild to moderate hepatic impairment. The range of Amias doses shown in the cost comparison chart was 2-16mg. The Panel noted the companies' submission that for each medicine depicted the same criteria had been applied with regard to the dose range depicted. The dose range for each medicine was clearly stated.

Of all the AIIRAs Amias had the lowest cost (£11.96) and the lowest maximum cost (£17.75). It was, however, not the least expensive antihypertensive. Lisinopril and enalapril (2.5mg) were £6.26 and £5.35 respectively and amlodipine was less expensive overall (£11.85 – £17.70).

The Panel considered that like was being compared with like. The cost comparison was not misleading as alleged. It was not unreasonable to include the 2mg dose of Amias. The dose of Amias had been clearly stated. No breach of the Code was ruled.

A general practitioner complained about a cost comparison which appeared in an Amias (candesartan) detail aid (reference TA 91011/AMS 5627) issued jointly by AstraZeneca UK Limited and Takeda UK Limited. Amias was an angiotensin II receptor antagonist (AIIRA).

On page 11 of the detail aid a bar chart which was headed 'Am I as competitively priced as other leading AII receptor antagonists? Comparative cost of 28 days' therapy' compared the cost of Amias 2-16mg with leading brands of AII receptor antagonists; valsartan 40-160mg, irbesartan 75-300mg, losartan 25-100mg; leading brands of ACE inhibitors, lisinopril 2.5-40mg, enalapril 2.5-40mg, and the leading brand of calcium antagonist, amlodipine 5-10mg.

COMPLAINT

The complainant stated that the bar chart purported to show a cost comparison of Amias against other antihypertensives but included a dose of Amias which was only used in exceptional circumstances and, indeed, was not even available in one month packs. Because this low 2mg dose was included on the bar chart the complainant believed it gave the misleading impression that Amias was better value than some of its competitors. The complainant had written to AstraZeneca several times about this and its responses had left him unsatisfied.

RESPONSE

AstraZeneca and Takeda submitted a joint response to the complaint. The companies were extremely concerned to learn that the complainant considered the cost comparison chart to be misleading. The bars on the chart illustrated the cost of 28 days' therapy with each of the leading brands of the AIIRAs and other leading brands of antihypertensive agents, across the full licensed dose range for each product.

Amias, as with other antihypertensives, was available in a range of doses allowing the prescriber to titrate the dose according to individual patient response and

clinical picture. Amias 2mg was the lowest dose of Amias and was indicated as the starting dose for patients with renal or hepatic impairment. Similarly, for example, the recommended starting dose for valsartan was 80mg, but a lower starting dose of 40mg was adopted in selected patient groups and, like Amias 2mg, valsartan 40mg was also available only in 7 day packs.

For each of the medicines for which costs were shown on the graph, the same criteria had been applied for the lower and upper limits of the costs of 28 days of treatment. The lower limit was the cost of 28 days of the lowest starting dose (or the lowest possible cost of 28 days of treatment where a higher dose would cost less – as for losartan). The upper limit was the cost of 28 days treatment at the maximum recommended dose. Many of the lowest doses were available as 7 day packs.

The companies noted that a comparison of the 'normal starting dose', 'usual maintenance dose', or 'maximum recommended dose' would show a very similar picture with respect to the relative costs of these agents. A summary of the relevant prices was provided.

The detail aid chart clearly stated that the agents shown were the leading brands either in the AIIRA class, ACE inhibitors or calcium antagonists and the doses were also clearly marked.

The companies thus contended that they had treated the information on cost for all of the other products featured in the same fashion as that for Amias.

The companies confirmed that they did not have formal written briefing materials relating to the particular page of the detail aid, representatives were verbally briefed on the use of the page in accordance with the information given above.

PANEL RULING

The Panel noted that the supplementary information to Clause 7.2 stated that price comparisons must be accurate, fair and must not mislead. Valid comparisons could only be made when like was compared with like.

The Panel noted that the left-hand page facing the cost comparison chart was headed 'A suitable choice for a wide range of hypertensive patients'. Four patient profiles were given including an elderly patient and one with some degree of renal impairment. Patients in either one of these two groups might require a reduced dose of Amias.

The Panel noted that the Amias summary of product characteristics stated that the starting dose was 4mg once daily. The usual maintenance dose was 8mg once daily and the maximum dose was 16mg once daily. An initial dose of 2mg was indicated in elderly patients with reduced renal or hepatic function and in patients with moderate to severe renal impairment or mild to moderate hepatic impairment. The range of Amias doses shown in the cost comparison chart was 2-16mg. The Panel noted the submission that for each medicine depicted the same criteria had been applied with regard to the dose range depicted. The dose range for each medicine was clearly stated.

The Panel noted that of all the AIIRAs Amias had the lowest cost (£11.96) and the lowest maximum cost (£17.75). The product, however, was not the least expensive antihypertensive. Lisinopril and enalapril (2.5mg) were £6.26 and £5.35 respectively and amlodipine was less expensive overall (£11.85 – £17.70).

The Panel considered that like was being compared with like; the cost comparison was not misleading as alleged. It was not unreasonable to include the 2mg dose of Amias. The dose of Amias had been clearly stated. No breach of Clause 7.2 of the Code was ruled.

Complaint received **5 June 2000**

Case completed **27 July 2000**

CLINICAL DIRECTOR v BAXTER HEALTHCARE, BAYER and WYETH

Advertisements in Haemophilia

The clinical director of a haemophilia centre complained about advertisements in the May edition of Haemophilia which appeared to be of US origin. Although it might be a storm in a teacup, the complainant's view was that US advertisements in what was clearly a British journal might lead to confusion to the reader, particularly if the latter happened to be a patient who suffered from haemophilia and needed guidance on current treatment.

Haemophilia informed the Authority that it was the official journal of the World Federation of Haemophilia. It was produced in English and published by Blackwell Science, which advised that the total circulation of 1,200 was split as follows: UK 8%, rest of Europe 38%, North America 32% and rest of the world 22%.

The first issue to be decided by the Panel was whether the advertisements were subject to the UK Code. The supplementary information to Clause 1 of the Code headed 'Journals with an International Distribution' stated that 'International journals which are produced in English in the UK are subject to the Code even if only a small proportion of their circulation is to a UK audience. It is helpful in these circumstances to indicate that the information in the advertisement is consistent with the UK marketing authorisation'. The Panel noted that Haemophilia was produced in English and distributed from the UK by its publishers. 8% of its circulation was to UK health professionals. The Panel considered that advertisements in the journal were therefore subject to the UK Code. The complainant's view that the advertisements might be confusing to patients was not considered relevant by the Panel as the journal was aimed at health professionals.

In Case AUTH/1034/6/00 an advertisement for Benefix with American prescribing information which referred to the Genetics Institute and Wyeth was taken up with Wyeth. The advertisement had been placed by the Genetics Institute in the US without the knowledge of Wyeth in the UK. It was an established principle under the Code that companies in the UK were responsible under the Code for the activities of their overseas parent company or divisions. The advertisement in question had been placed by the Genetics Institute which was part of Wyeth. Wyeth in the UK was therefore responsible under the Code for the advertisement. The Panel noted that whilst the prescribing information in the advertisement was consistent with the European marketing authorization, it did not meet all the requirements of the Code. A breach was ruled.

In Case AUTH/1035/6/00, advertisements for Feiba VH and Recombinate had been placed by Baxter in the US without approval by Baxter Healthcare in the UK. Baxter Healthcare in the UK was responsible under the Code. The prescribing information did not meet the requirements of the Code and a breach was ruled.

In Case AUTH/1036/6/00, an advertisement for Kogenate placed by Bayer in the US was taken up with Bayer in the UK which was responsible under the Code. The prescribing information did not meet the requirements of the Code and a breach was ruled.

COMPLAINT

The clinical director of a haemophilia centre submitted a complaint about advertisements that appeared in the May edition of Haemophilia. The complainant stated that advertisements in the journal seemed to be of US origin. Although this might be a storm in a teacup, the complainant felt that US advertisements in what was clearly a British journal might lead to confusion to the reader, particularly if the latter happened to be a patient who suffered from haemophilia and needed guidance on current treatment.

When writing to the companies concerned, attention was drawn to the requirements of Clause 4.1 and the supplementary information to Clause 1.1 of the Code.

The Authority contacted Haemophilia and was advised that it was the official journal of the World Federation of Haemophilia. It was produced in English and published by Blackwell Science, which advised that the total circulation of 1,200 was split as follows: UK 8%, rest of Europe 38%, North America 32% and rest of the world 22%.

Case AUTH/1034/6/00

An advertisement for Benefix with American prescribing information which referred to the Genetics Institute and Wyeth was taken up with Wyeth.

RESPONSE

Wyeth explained that Benefix was marketed in the UK by Baxter Healthcare Ltd and there was no connection between Wyeth UK and Baxter with regard to the promotion of this product in the UK.

The marketing authorisation was gained through the centralised procedure and the marketing authorization holder was the Genetics Institute in Germany. Although the Genetics Institute and Wyeth were both divisions of American Home Products, Wyeth was not involved in any way in the sale or promotion of this product in the UK.

The matter was followed up with Wyeth which was informed that Baxter Healthcare had advised the Authority that in the US Benefix was promoted by the Genetics Institute which was part of Wyeth. Baxter Healthcare had explained that the marketing rights had been granted to Baxter Hyland Immuno in Europe. The advertisement in question had been placed by the Genetics Institute. Wyeth stated that the advertisement for Benefix was placed without the

knowledge of Wyeth by the Genetics Institute in the US; Wyeth would brief its US colleagues with regard to the implications of their actions from a UK Code perspective.

Whilst Wyeth acknowledged the requirements of the ABPI Code with regard to UK produced journals with an international distribution, and acknowledged that Haemophilia was printed in the UK, the company asked the Panel to consider that only 8% of the journal circulation was in the UK.

Wyeth believed that for the Panel to conclude that the Code did apply in this case would be a very strict interpretation of the supplementary information to Clause 1.1.

If however the Panel concluded that the Code did apply, it would draw its attention to the fact that the professional prescribing information accompanying the advertisement was consistent with the European marketing authorization for the product and met most (but not all) of the requirements of Clause 4.1.

Wyeth was somewhat puzzled by the complainant's view that '…US advertisements in what was clearly a British Journal might lead to confusion to the reader, particularly if the latter happened to be a patient …'. Not only was it unlikely that a patient would have easy access to a journal of this kind, but the product was available in the UK and, generally speaking, haemophilia patients (and carers) were remarkably aware of all issues and treatments surrounding their conditions.

PANEL RULING

The Panel noted that the first issue to be decided was whether the advertisement was subject to the UK Code. The supplementary information to Clause 1.1 headed 'Journals with an International Distribution' stated that 'International journals which are produced in English in the UK are subject to the Code even if only a small proportion of their circulation is to a UK audience. It is helpful in these circumstances to indicate that the information in the advertisement is consistent with the UK marketing authorization'.

The Panel noted that Haemophilia was produced in English and distributed from the UK by its publishers, Blackwell Science. 8% of its circulation was to UK health professionals. The Panel considered that advertisements in the journal were therefore subject to the UK Code.

The complainant's view that the advertisement might be confusing to patients was not considered relevant by the Panel as the journal was aimed at health professionals.

The Panel noted that the advertisement was placed in the journal without the knowledge or authority of Wyeth in the UK. The Panel noted that it was an established principle under the Code that companies in the UK were responsible under the Code for the activities of their overseas parent company or divisions. The advertisement in question had been placed by the Genetics Institute in the US which was part of Wyeth. Wyeth in the UK was therefore responsible under the Code for the advertisement.

The Panel noted that Clause 4.1 required prescribing information to appear on all promotional material; the content of prescribing information was set out in Clause 4.2. The Panel noted that whilst the prescribing information in the advertisement was consistent with the European marketing authorization it did not meet all the requirements set out in Clause 4.2. The advertisement was therefore in breach of Clause 4.1 and a breach of that clause was ruled.

Case AUTH/1035/6/00

Advertisements for Feiba VH and Recombinate which contained American prescribing information were taken up with Baxter Healthcare Ltd.

RESPONSE

Baxter Healthcare stated that the advertisements were placed by its US company, which did not submit the proofs for its attention prior to publication. Baxter Healthcare understood that the advertisements were meant for a US audience, who were known to subscribe to this journal. Given the limited population of physicians who specialised in haemophilia, it was natural that a journal that was so specific would have to be by nature an international journal. It was its understanding that its colleagues in the US viewed this to be the case and, therefore, the supplementary information to Clause 1.1 of the Code might be appropriate in that the advertisements were in compliance with the IFPMA Code.

This had to be the core of the complaint and as the publisher, it would seem, did not raise this matter with the advertiser then there was a need for clarification for all concerned.

PANEL RULING

The Panel considered that its general comments above about the supplementary information to Clause 1.1 and the activities of overseas divisions at Case AUTH/1034/6/00 also applied here. The advertisements were subject to the UK Code and Baxter Healthcare in the UK was responsible for the Feiba VH and Recombinate advertisements. A breach of Clause 4.1 was ruled.

Case AUTH/1036/6/00

An advertisement for Kogenate placed by Bayer in the US was taken up with Bayer plc, Pharmaceutical Division, in the UK.

RESPONSE

As the journal was published in the UK Bayer accepted that it was in breach of the Code. Bayer instructed its US colleagues to withdraw the advertisement from future editions.

Bayer pointed out that although the Code noted that it applied to the advertising of medicines in professional journals which were produced in the UK and/or intended for a UK audience, only 8% of this particular journal's circulation was in the UK. The remaining 92% was supplied to other countries throughout the world. Bayer therefore submitted that

the intended audience was not the UK but acknowledged that there was a provision within the Code for journals produced in the UK.

As this advertisement, together with others placed by US based companies, would appear in other international journals published outside of the UK, such as Thrombosis and Haemostasis, Bayer asked that this matter be raised with the ABPI Board for its consideration. Bayer submitted that the global nature of some pharmaceutical products warranted a realistic and pragmatic approach to complaints of this nature.

Moreover, Bayer considered it ironic that the very same specialists would see this advertisement in Thrombosis and Haemostasis, without Bayer plc being in breach of the Code, as it was produced outside the UK and subject to other advertising guidelines.

Bayer did not accept the complainant's contention that UK physicians would be confused by the advertisement. This journal was a specialist journal that was received by a relatively small body of physicians specialising in the treatment of patients with haemophilia. These physicians would be aware of recombinant factor concentrates available in the UK and US and would be aware of products that were in late stage research and development. Moreover, Bayer did not accept the proposition that patients would read this journal themselves. The journal was intended for physicians treating haemophilia and not patients *per se*. Bayer considered this point to be irrelevant and without bearing on this matter.

PANEL RULING

The Panel considered that its general comments above about the supplementary information to Clause 1.1 and the activities of overseas divisions at Case AUTH/1034/6/00 also applied here. The advertisement was subject to the UK Code and Bayer in the UK was responsible for the Kogenate advertisement.

The Panel noted that the company accepted that a breach of Clause 4.1 had occurred and it had instructed its US colleagues to withdraw the advertisement from future publications. A breach of Clause 4.1 was ruled.

Complaint received	**6 June 2000**
Cases completed	
Case AUTH/1034/6/00	**12 October 2000**
Case AUTH/1035/6/00	**10 October 2000**
Case AUTH/1036/6/00	**3 October 2000**

CONSULTANT OPHTHALMIC SURGEON v ASTA MEDICA

Optilast mailing

A consultant ophthalmic surgeon complained about a mailing for Optilast (azelastine) entitled 'The pick of the bunch at a low cost' which had been sent by Asta Medica. Part of the mailing had the subheading 'Lowest script costs of the leading eye drop brands' and featured a 28 day cost comparison of the leading eye drop brands. Optilast was shown as the least expensive option (£6.88) while the cost of sodium cromoglycate was given as £7.96.

The complainant noted that Optilast was being promoted on the basis of cost, amongst other criteria, and that a comparative price for sodium cromoglycate had been given as £7.96. The complainant accepted that one brand of sodium cromoglycate, Opticrom, did cost £7.96/28 days but another brand, Hay-Crom, cost only £4.40 and the BNF gave a net price of £2.68 for the various rival formulations. The complainant stated that it had not been made clear why the most expensive version of sodium cromoglycate had been selected for comparison but it seemed likely that this was a deliberate attempt to mislead the medical professional.

The Panel noted that the cost comparison chart was clearly labelled as comparing the price per 28 days' treatment of leading brand eye drops for the treatment of seasonal allergic conjunctivitis. The page on which the chart appeared included a subheading 'Lowest script costs of the leading eye drop brands'. Asta Medica had submitted with regard to sodium cromoglycate that Opticrom was the brand most frequently chosen by NHS prescribers and the company had data showing that more packs of Opticrom were sold than packs of Hay-Crom. The Panel did not therefore accept the allegation that the chart was misleading. No breach of the Code was ruled. The Panel noted that the Code prohibited companies from using the brand names of other companies' products unless the prior consent of the proprietors had been obtained.

A consultant ophthalmic surgeon complained about an Optilast (azelastine) mailing (ref OPTI.992.03.00) sent to selected general practitioners and hospital-based ophthalmologists by Asta Medica Limited. The mailing was entitled 'The pick of the bunch at a low cost'. One part of the mailing had the subheading 'Lowest script costs of the leading eye drop brands' and featured a 28 day cost comparison of the leading eye drop brands. Optilast was shown as the least expensive option (£6.88) while the cost of sodium cromoglycate was given as £7.96. The cost comparison chart was referenced to MIMS, March 2000.

COMPLAINT

The complainant noted that Optilast was being promoted on the basis of cost, amongst other criteria, and that a comparative price for sodium cromoglycate had been given as £7.96. The complainant accepted that one brand of sodium cromoglycate, Opticrom, did cost £7.96/28 days but another brand, Hay-Crom, cost only £4.40 and the BNF gave a net price of £2.68 for the various rival formulations.

The complainant stated that it had not been made clear why the most expensive version of sodium cromoglycate had been selected for comparison but it seemed likely that this was a deliberate attempt to mislead the medical professional.

RESPONSE

Asta Medica stated that, in anticipation of the hayfever season the mailing was produced to remind a selected group of doctors that the company had a unique product for the treatment of seasonal allergic conjunctivitis. In addition, the price of Optilast was compared with the prices of the leading branded products currently prescribed for this condition. The text accompanying the cost comparison bar chart which appeared in the mailing was headed, 'Lowest script costs of the leading eye drop brands' and was referenced MIMS March 2000. In addition, the statement referring to leading brand comparisons was repeated immediately below in the title of the bar chart and therefore appeared twice on the same page.

Asta Medica provided data to show that between May 1999 and April 2000 over 18 times as many packs of Opticrom were sold compared to packs of Hay-Crom. The cost to the NHS incurred by the prescribing of Hay-Crom was, therefore, negligible when compared to the cost incurred through the prescribing of Opticrom. On this basis Asta Medica stated that it had opted to compare the cost of using its product, Optilast, with the product most frequently chosen by NHS prescribers, ie Opticrom.

Asta Medica stated that it did not accept the assertion that it was attempting to mislead the medical professional as the text stated clearly on the appropriate page of the mailing that the prescription costs of the leading eye drop brands were being compared. Further, the price of Optilast had been compared with the price of what was by far the most commonly prescribed branded sodium cromoglycate product (Opticrom) and finally the basis of the cost comparison was made clear in the mailing, and as the choice of competitor products was consistent with this basis, there was no justification for describing the mailing as misleading.

PANEL RULING

The Panel noted that the cost comparison chart was clearly labelled as comparing the price per 28 days' treatment of leading brand eye drops for the treatment of seasonal allergic conjunctivitis. The page on which the chart appeared included a subheading 'Lowest script costs of the leading eye drop brands'.

The Panel noted Asta Medica's submission that with regard to sodium cromoglycate, Opticrom was the brand most frequently chosen by NHS prescribers and the company had data showing that more packs of Opticrom were sold than packs of Hay-Crom. The Panel did not therefore accept the allegation that the chart was misleading. No breach of Clause 7.2 of the Code was ruled.

The Panel noted that Clause 7.10 of the Code prohibited companies from using the brand names of other companies' products unless the prior consent of the proprietors had been obtained.

During its consideration of this case the Panel noted that the mailing included an offer of a free pair of Optilast sunglasses. The Panel queried whether this met with the requirements of Clauses 18.1 and 18.2 of the Code and the supplementary information that promotional aids cost the company no more than £5 (excluding VAT) and that the item had to be relevant to the practice of the recipient's profession. The Panel did not consider that providing a pair of sunglasses was appropriate. The Panel requested that the matter be taken up with Asta Medica in accordance with Paragraph 16 of the Constitution and Procedure (Case AUTH/1049/7/00).

Complaint received **12 June 2000**

Case completed **13 July 2000**

CASE AUTH/1040/6/00

LILLY v NOVO NORDISK

NovoPen 3 mailing and helpline

Lilly complained about a letter and a leaflet which had been sent to patients by Novo Nordisk. The letter was headed 'Information for people using insulin' and stated, *inter alia*, 'The NovoPen 3 system has been designed to make life with injections as easy and simple as possible – it is a portable, convenient and very discreet way to take insulin that can help you become more independent and in control of your diabetes'. Recipients were informed that if they were interested in receiving further information on NovoPen 3 they could return an enclosed reply card or contact the NovoPen 3 Helpline; they would receive a video which demonstrated the device and included interviews with patients and their specialist nurses. The accompanying leaflet was headed 'NovoPen 3. The discreet, convenient insulin delivery system you can take anywhere.' The leaflet described injections with NovoPen 3 as 'virtually pain free'.

Lilly pointed out that the letter contained the slogan 'Anyone, Anytime, Anywhere' and was clearly branded by Novo Nordisk. It also contained promotional information about the NovoPen range. Although devices were not covered by the Code, Lilly believed that there was a clear breach of the Code in that the materials advertised to the public and would induce them to request a specific medicine. In view of the serious nature of this matter, a breach of Clause 2 was also alleged in that it brought discredit to the industry. The reason Lilly believed promoting the NovoPen 3 directly to patients to be in breach of the Code was because it could only be used with Novo Nordisk insulins. Novo Nordisk was encouraging patients to ask for the NovoPen 3, which in many cases would require a change of insulin from another manufacturer. In addition, any discussion of modern pen devices that only covered NovoPen 3 was not a 'balanced' representation. Contacting the helpline raised further concerns. No warning was given that a change in insulin might be required. Even when it was clearly stated that Humulin M3 (which was not compatible with NovoPen 3) was currently being prescribed, the Novo Nordisk helpline did not advise that a change in insulin would be required. Despite this, Novo Nordisk still offered to send out details of how to obtain a NovoPen 3.

Lilly's allegations regarding the written materials had much in common with those in an earlier complaint, Case AUTH/1018/4/00. In that case breaches of the Code ruled by the Panel were confirmed on appeal to the Code of Practice Appeal Board. Those aspects already dealt with were not further proceeded with in the present case. The previous case had not covered Lilly's allegation that any discussion of modern pen devices which only covered NovoPen 3 was not a balanced representation nor Lilly's concerns about the helpline nor the alleged breach of Clause 2. These matters therefore remained to be considered.

The Panel examined two scripts for the helpline. One was for follow up on people who had responded to the original mailing. The responders were contacted to ask for views on the video. An agreement to call was discussed at the time the video was requested. Those called were told that the company was building a profile of insulin users and were asked for details about their diabetes and insulin use. They were asked whether they would be interested in using NovoPen 3 and what was the percentage likelihood of them going to ask for NovoPen 3. The second script was for following up non-responders. Those called were asked about who had diabetes and referred to the video which it was stated gave a full explanation of NovoPen 3 and demonstrates '… how easy and convenient it is to use and includes commentary from diabetic specialist nurses and people who use insulin'. A copy of the video was offered. If the person called asked how to obtain NovoPen 3 the response was to contact the diabetic specialist nurse who would '… be able to arrange for you to be able to be provided with one' as would the nearest clinic. The Panel considered that the helplines constituted promotion of Novo Nordisk's insulins to the general public and would encourage members of the public to ask their

doctors to prescribe the NovoPen 3 device and, in effect, a Novo Nordisk insulin cartridge. The Panel therefore ruled breaches of the Code. With regard to the alleged breach concerning the lack of balance, the Panel considered that although this was a new allegation the rulings in the previous case were relevant and a breach of the Code was ruled. In relation to the alleged breach of Clause 2, the Panel noted that this was used as a sign of particular censure and reserved for such circumstances. The Panel did not consider that the circumstances warranted such a ruling.

Eli Lilly and Company Limited complained about a mailing sent by Novo Nordisk Pharmaceuticals Ltd to patients. The mailing consisted of a letter and a leaflet which referred to a video. The letter was headed 'Information for people using insulin' and stated, *inter alia*, 'The NovoPen 3 system has been designed to make life with injections as easy and simple as possible – it is a portable, convenient and very discreet way to take insulin that can help you become more independent and in control of your diabetes'. Recipients were informed that if they were interested in receiving further information on NovoPen 3 they could return an enclosed reply card or contact the NovoPen 3 Helpline; they would receive a video which demonstrated the device and included interviews with patients and their specialist nurses. The accompanying leaflet was headed 'NovoPen 3. The discreet, convenient insulin delivery system you can take anywhere.' The leaflet described injections with NovoPen 3 as 'virtually pain free'.

COMPLAINT

Lilly pointed out that the letter contained the slogan 'Anyone, Anytime, Anywhere' and was clearly branded by Novo Nordisk. It also contained promotional information about the NovoPen range.

Lilly noted that although devices were not covered by the Code it believed that there was a clear breach of Clause 20.1 of the Code in that the materials advertised to the public and would induce them to request a specific medicine. Also, in view of the serious nature of this matter, a breach of Clause 2 was alleged in that it brought discredit to the industry.

The reason Lilly believed promoting the NovoPen 3 directly to patients to be in breach of the Code was because it could only be used with Novo Nordisk insulins. Novo Nordisk was encouraging patients to ask for the NovoPen 3, which in many cases would require a change of insulin from another manufacturer to the specific use of Novo Nordisk insulins. In addition, any discussion of modern pen devices that only covered NovoPen 3 was not a 'balanced' representation, as demanded by the supplementary information.

Lilly stated that contacting the patient information number, given on the letter, raised further concerns. No warning was given that a change in insulin might be required. Even when it was clearly stated that Humulin M3 (which was not compatible with NovoPen 3) was currently being prescribed, the Novo Nordisk helpline did not advise that a change in insulin would be required. Despite this, Novo Nordisk still offered to send out further promotional literature and information about how to obtain a NovoPen 3.

Lilly had already received complaints from very dissatisfied health care professionals that patients had been asking for the NovoPen in response to this campaign. They were also expressing concern that this campaign would put additional unnecessary strains on an already overburdened diabetes service.

On receipt of this complaint the Authority advised Novo Nordisk that the allegations regarding Clauses 20.1 and 20.2 concerning the written materials were closely similar to those which had been the subject of the recent Panel adjudication in Case AUTH/1018/4/00 wherein the parties had been advised of the Panel's rulings and either party could decide to accept the rulings or appeal them to the Appeal Board.

The Authority referred to Paragraph 5.1 of the Constitution and Procedure which stated, *inter alia*, that if a complaint concerned a matter closely similar to one which had been the subject of a previous adjudication the Director should normally allow the complaint to proceed if it was not the subject of appeal to the Code of Practice Appeal Board. In accordance with Paragraph 5.1 of the Constitution and Procedure the Director therefore awaited the decisions with regard to appeals in Case AUTH/1018/4/00 before deciding whether this part of Lilly's complaint should proceed.

In addition to the allegations dealt with in Case AUTH/1018/4/00 Lilly also alleged that any discussion of modern pen devices that only covered NovoPen 3 was not a balanced representation as demanded by the supplementary information. Lilly also referred to contact with the patient information helpline and, further, alleged a breach of Clause 2 of the Code. It was these aspects which now needed to be addressed irrespective of the outcome in Case AUTH/1018/4/00.

RESPONSE

Novo Nordisk stated that the complainant had two concerns; that the video was not balanced and factual (Clause 20.2) and that the activity of mailing information about NovoPen 3 brought the industry into disrepute (Clause 2).

Approximately two weeks after Lord Hunt's announcement regarding the availability of certain insulin delivery devices and needle devices on NHS prescription, Novo Nordisk sent a mailing to 15,000 randomly selected households which had indicated in a consumer products survey that someone in the household had diabetes. The database was held by a company specialised in consumer databases and all responders to the consumer products survey questionnaire had the option of allowing information about them to be passed to third parties. To the best of Novo Nordisk's knowledge and belief, no mailing was sent to anyone who had indicated an unwillingness to receive communication from third parties. The names and addresses of the intended recipients were not known to Novo Nordisk.

Following a very high response rate with positive feedback from patients from the pilot mailing (and prior to the ruling on Case AUTH/1018/4/00), the mailing was sent to a further 155,000 people on this same database. It was after this second mailing that the complaint from Lilly was received.

Novo Nordisk stated that the first complaint dealt with the question of 'balanced representation' with the video on NovoPen 3. As previously stated in the response to Case AUTH/1018/4/00, the company believed that the Code did not cover the promotion of devices which could use a wide variety of products – albeit from one manufacturer. It was certainly not explicit in the Code or in the supplementary information. It was a fact that all current 3ml insulin devices were only suitable for one manufacturer's insulins. The BD Pen should only be used with Lilly insulins and the Optipen should only be used with Aventis insulins.

Novo Nordisk submitted that the need to give a balanced discussion of all devices did not therefore apply and that it was only obliged to give factual and balanced information about its insulin delivery device. A transcript of the video was provided. Only the questions were scripted because real patients were used and it had no control over the answers. For convenience, the transcript had been completed to include their answers but with the 'erms and ers' removed. The video consisted generally of patients and nurses relating their own experiences without being instructed or prompted. This was supplemented with factual information about the rationale for developing the insulin pen and instructions for the use of NovoPen 3. It made no claims about the ability to improve their control or benefit them medically. It concentrated on patients' fears about syringes and injections in general and focused on simplicity of use and discreetness. The video was initially designed for patients who might be afraid of starting insulin therapy or for people who did not know an alternative to syringes was now available to them at no cost.

In Europe there had been direct to consumer awareness campaigns for several years with devices (eg France, Ireland and Germany) which had caused no concern to the European authorities because a specific medicinal product was not mentioned. The European Council Directive on the advertising of medicinal products for human use was the controlling legislation in this field and its overarching rationale and aim was that public health was enhanced by the provision of appropriate information about medicinal products and health. Consistent with this, patients must be protected from 'excessive and ill considered claims' about medicinal products. Factual information that related directly or indirectly to products was allowed provided it contained no claims concerning a specific medicinal product. It was implicit that manufacturers had a role in health education but in relation to information supplied direct to the public the law reflected the fact that care should be taken to avoid undermining the doctor/patient relationship. That relationship would be undermined by direct promotion of a specific prescription-only medicine that encouraged a patient to have a preconceived notion of what product was needed to treat the patient's condition and consequently to ask the doctor for that specific medicinal product.

Novo Nordisk submitted that it was against this rationale and these considerations that the individual provisions of the UK regulations and the Code, that reflected the law and good practice, must be interpreted. The law also recognised that restrictions on advertising and therefore of freedom of speech must be proportionate to the aim of the law in protecting public health. Novo Nordisk respectfully suggested that this consideration was particularly important in today's environment where a less paternalistic attitude to healthcare was seen as appropriate and patients' thirst for information about products was gradually being met through the provision of information in the form of detailed leaflets, European Public Assessment Reports, access to the ABPI Compendium of Data Sheets and Summaries of Product Characteristics, and health education campaigns – all of which the ABPI had encouraged.

Novo Nordisk believed that it was against this background that one must consider whether information about a medical device (the advertising of which in principle was not forbidden) to deliver a range of medicines, but which did not focus on a specific medicinal product, should be judged. This was particularly so when the patient population at whom the information was directed – in this case people with diabetes – could reasonably be expected to have been advised by doctors on their need for insulin and what specific product was appropriate for each of them. Such patients would have a relatively sophisticated understanding of the medicines themselves but might not have the same knowledge about advances in technology in relation to the delivery of insulins and changes in the reimbursement system. Could it really sensibly be suggested that by alerting patients to the existence of alternative methods of delivering Novo Nordisk insulins the doctor/patient relationship would be undermined, and with it public health, in any way at all? It made no reference to a specific medicinal product; it made no claims related to a specific medicinal product (it even deleted the name of the particular product on the example of a cartridge in the picture) and it had not sought to undermine the doctor/patient relationship in any way. On the contrary, Novo Nordisk respectfully suggested that to stop manufacturers promoting the devices by which their products could be administered would be wholly disproportionate to the rationale of the legislation and the Code. Far from protecting patients, such an interpretation of the rules actually constituted a perpetuation of a paternalistic approach to information for patients that was neither required nor appropriate under the legislation and Code.

Novo Nordisk submitted that the aim with this mailing, in the light of the Government's announcement regarding reimbursement of devices and needles, was to make people on Novo Nordisk insulin vials aware that an alternative method of delivery was now available because many people in

the past had avoided pen delivery systems owing to the cost of the needles. Novo Nordisk agreed with the Q and A from the ABPI's own Informed Patient Initiative Task Force which stated that 'A better informed and managed patient with a chronic condition eg diabetes, is likely to stay clear of debilitating complications…'

In consultation with Diabetes UK (formerly the British Diabetic Association) specifically on this issue, Novo Nordisk had been informed that, while it wholly supported the ABPI Code (as did Novo Nordisk), it also endorsed information being made available to patients.

In light of the above arguments on the legislation, device-advertising activities in Europe and comments made by the chief executive of the leading patient organisation for people with diabetes in the UK, Novo Nordisk failed to appreciate how providing such information could possibly be seen as bringing the industry into disrepute.

* * * * *

Novo Nordisk decided to appeal the Panel's ruling in Case AUTH/1018/4/00 whereupon the Appeal Board upheld the Panel's rulings of breaches of Clauses 20.1 and 20.2 of the Code. The allegations concerning Clauses 20.1 and 20.2 in relation to advertising to the public and inducing them to request a specific medicine had now been the subject of an adjudication by the Code of Practice Appeal Board. In accordance with Paragraph 5.1 of the Constitution and Procedure, the Director decided that this part of Lilly's complaint should not proceed.

FURTHER RESPONSE

Novo Nordisk stated that all were familiar with the issues surrounding the promotion of insulin pen devices and Novo Nordisk had agreed to abide by the Appeal Board's decision, but believed the decision to be fundamentally incorrect and might be unlawful in the light of recent European legislation. In considering the points raised it should be remembered that at no time did Novo Nordisk consider this promotion to be covered by the Code since it did not then, and still did not now, believe that it was promoting a specific medicinal product and therefore it did not feel any compulsion to list all manufacturers' pens in the mailing. It did however indicate on page 2 of the leaflet sent with the letter that 'insulin pens and cartridges are available from several manufacturers'.

Regarding the allegation about the telephone information helpline, Novo Nordisk clearly could not trace one specific call and know who said what to whom with any degree of accuracy.

However the complaint from Lilly seemed to imply that it would be possible for a patient to obtain a NovoPen 3 without a healthcare professional being involved, which was simply not so. It would not be possible for a patient who was on another manufacturer's insulin to obtain a NovoPen 3 except via a healthcare professional who would take the responsibility for the prescription and therefore be knowledgeable about the compatibilities of different insulin devices and their insulins (otherwise they would not write the prescription but refer to an experienced colleague). Novo Nordisk therefore did not see how this could possibly raise concerns since, having discussed this externally and also from in-house expertise, it knew that if a patient discussed a device with a healthcare professional they would be given a device that would suit their insulin and not an insulin to suit the device, since the insulin was the prescription and the device was merely a way of administering this prescription. The telephone helpline was run by another organisation on its behalf. The telephone operatives used a script, a copy was provided. They were not allowed to deviate from the script and a provision for mid-call transfer to the Novo Nordisk Customer Care Centre was available for any patients who required specific information not covered by the script. Initially a few non-responders were contacted but this ceased during the appeal process in Case AUTH/1018/4/00.

Novo Nordisk stated that Clause 2 was reserved for a very serious breach and it did not feel that it had breached the Code at all, although it appreciated that some aspects of this promotion, with the benefit of hindsight, could have been done differently. Novo Nordisk believed that this situation had never occurred before and was therefore something of a test case. It would understand the allegation of a breach of Clause 2 if had flagrantly breached a well-established guideline which was clearly covered by the current Code but this was simply not so. Novo Nordisk still believed that its rights under European law to promote its devices had been infringed by the Appeal Board ruling since it could not see the mischief in this promotion. It might be of some interest to know that the mailing was extremely well received by patients, indicating a need for more information to be provided by manufacturers rather than less and for this reason Novo Nordisk submitted that, far from bringing the industry into disrepute, it had actually taken some positive steps to provide information for a patient group that had shown a clear need for such information to be provided.

PANEL RULING

The Panel noted that in Case AUTH/1018/4/00 the Appeal Board had ruled that the mailing and the video constituted promotion of Novo Nordisk's eight insulins to the general public and upheld the Panel's ruling of a breach of Clause 20.1 of the Code. The materials would direct the public towards specific medicines produced by Novo Nordisk and would thus encourage members of the public to ask their doctors to prescribe the NovoPen 3 device and in effect a Novo Nordisk insulin cartridge. The Appeal Board also upheld the Panel's ruling of a breach of Clause 20.2 of the Code. The Panel noted that the Director had decided that in accordance with Paragraph 5 of the Constitution and Procedure it was not necessary to consider Lilly's allegations of breaches of Clauses 20.1 and 20.2 with regard to the matters already ruled upon which had been subject to appeal.

With regard to the alleged breach of Clause 20.2 concerning the lack of balance, the Panel considered

that although this was a new allegation the rulings in the previous case were relevant and a breach of Clause 20.2 was ruled.

The Panel considered the alleged breach of Clause 2. The Panel noted that Clause 2 of the Code was used as a sign of particular censure and reserved for such circumstances. The Panel did not consider that the circumstances warranted such a ruling and no breach of Clause 2 was ruled.

With regard to the patient helpline, the Panel accepted that it was difficult for Novo Nordisk to respond to an allegation concerning one enquiry. The Panel examined the two scripts. One was for follow up on people who had responded. The responders were contacted to ask for views on the video. An agreement to call was discussed at the time the video was requested. Those called were told that the company was building a profile of insulin users and were asked for details about their diabetes and insulin use. They were asked whether they would be interested in using NovoPen 3 and what was the percentage likelihood of them going to ask for NovoPen 3. The second script was for following up non-responders. Those called were asked about who had diabetes and referred to the video which it was stated gave a full explanation of NovoPen 3 and demonstrates '… how easy and convenient it is to use and includes commentary from diabetic specialist nurses and people who use insulin'. A copy of the video was offered. If the person called asked how to obtain NovoPen 3, the response was to contact the diabetic specialist nurse who would '… be able to arrange for you to be able to be provided with one' as would the nearest clinic.

The Panel considered that the helplines constituted promotion of Novo Nordisk's insulins to the general public and would encourage members of the public to ask their doctors to prescribe the NovoPen 3 device and, in effect, a Novo Nordisk insulin cartridge. The Panel therefore ruled breaches of Clauses 20.1 and 20.2 of the Code.

Complaint received **16 June 2000**

Case completed **16 October 2000**

CASE AUTH/1041/6/00

CONSULTANT PHYSICIAN v GLAXO WELLCOME

Payment to attend workshop

A consultant physician complained about an invitation which he had received from Glaxo Wellcome to attend an 'Epilepsy Workshop 2000' which would last two hours. The invitation stated that the company would share the latest information about antiepileptic medicines, the management of the disease and 'hear your thoughts regarding the unmet needs of general physicians treating patients with epilepsy'. A consultant neurologist was to chair the workshop and the audience would be divided into syndicate groups to discuss issues in the management of women with epilepsy. The invitation referred to the need for preparatory work exploring the invitees' needs in terms of information about the therapy area, the treatments available and management of people with epilepsy in general. An honorarium of £150 was to be paid for the time and participation together with reimbursement of travel expenses. Invitations were on a first come, first served basis. It was alleged that the financial inducement to attend was in breach of the Code.

The Panel accepted that there was a difference between holding a meeting for health professionals and employing health professionals to act as consultants to a company. The selection of consultants should stand up to independent scrutiny. A number of previous cases were referred to.

The Panel noted the purpose of the workshop from the invitation. Twelve workshops had been held at various locations in England and Scotland. The company had invited 113 general physicians. Eleven had accepted to attend the meeting in question. In the Panel's view it was questionable whether all the attendees would have truly acted as consultants to the company each giving such advice as to justify a £150 honorarium and reimbursement of travel expenses. The Panel considered that it was not unacceptable for companies to pay healthcare professionals and others for advice as to how products should be promoted. It was a question of deciding where the boundary lay. The Panel noted the reasons submitted by Glaxo Wellcome for the need to investigate the management of epilepsy by general physicians and for investigating the regional differences and the effect that these had on patient management. The Panel was, however, concerned about the overall arrangements for the meetings, including the number of meetings and the fact that places were allocated on a first come, first served basis. The invitation was not clear about the expected role of participants. The Panel noted that the participants were asked to undertake some pre-reading. The meeting itself lasted just less than two hours. During that time the participants listened to the chairman's update for 30 minutes, this was followed by 45 minutes of syndicate work. The discussion, summary, conclusion and dinner were allocated a total of 30 minutes. The Panel considered that overall the meeting constituted a promotional meeting. Reference was made to a number of treatments including Glaxo Wellcome's product. It was not appropriate to pay doctors to attend such meetings. A breach of the Code was ruled.

COMPLAINT

A consultant physician complained about an invitation from Glaxo Wellcome UK Limited to attend a workshop.

The invitation referred to 'Epilepsy Workshop 2000' which would last two hours. Invitees were told that the company would share the latest information about antiepileptic medicines, the management of the disease and 'hear your thoughts regarding the unmet needs of general physicians treating patients with epilepsy'. A consultant neurologist was to chair the workshop and the audience would be divided into syndicate groups to discuss issues in the management of women with epilepsy. The invitation referred to the need for preparatory work exploring the invitees' needs in terms of information about the therapy area, the treatments available and management of people with epilepsy in general. An honorarium of £150 was to be paid for the time and participation together with reimbursement of travel expenses. Invitations were on a first come, first served basis.

The complainant had previously declined a similar invitation to another epilepsy workshop which also offered a financial inducement to attend. A breach of Clause 19 was alleged.

RESPONSE

Glaxo Wellcome stated that the invitation was for a workshop to be held at the Devonshire Hotel, Glasgow, on 27 June 2000. This was the last in a series of twelve such workshops, which had been held in England and Scotland.

Glaxo Wellcome stated that its product Lamictal (lamotrigine) had been available in the UK for the treatment of simple and complex partial seizures and primary and secondary generalised tonic-clonic seizures for ten years. In this time, its main focus of promotion had been neurologists, learning disability specialists and paediatricians. For the past two years the company had included in its list of key customers general physicians who, in the UK, treated the majority of newly diagnosed patients with epilepsy in secondary care.

As part of the plans to include general physicians in its key customer groups, Glaxo Wellcome wished to develop a clear understanding of their management of patients with epilepsy. It was aware that the organisation of services for the management of patients with epilepsy varied between hospitals and regions. The number of neurology units per head of population on a regional basis varied, for example, from 1,300 population per neurology unit in the North West of England region to as much as 5,350 population per unit in the Eastern region. This had an impact on the role of the general physician in treating epilepsy and the configuration of the service provided. For example, some general physicians might only see one or two patients with epilepsy a month. Others had specifically arranged outpatient clinics for epilepsy. The question to be answered was what effect this regional variation might have on the actual management patients received. It wanted to evaluate the current thoughts of general physicians regarding the management of epilepsy and specifically their views on the management of women with epilepsy (as part of the company's current promotional focus in women), compared with that of the treating hospital specialists (neurologists and learning disability physicians). The gathering of this information on a regional basis was therefore key to its understanding of the current market place. This information was not otherwise available to Glaxo Wellcome. This was the purpose of setting up a series of twelve regional interactive workshops.

This particular workshop in question was to be chaired by a specialist registrar in neurology and neurophysiology. The chairman was selected from the company's list of key neurologist opinion leaders. As the company had had insufficient contact with general physicians to be able to specifically target individuals, the invitees were selected from a hospital electronic database using the selection criteria of all local general physicians with an interest in epilepsy. Using these filters, the database produced a list of general physicians, including general medical consultants, specialist registrars, and care of the elderly consultants and specialist registrars. As it had limited promotional contact with general physicians and wished to develop a broad understanding of the treatment issues in epilepsy, there were no other criteria employed to sub-select individuals. To have done so might have led to a loss of the broad perspective and a loss of the effects of the wide variation of patient management especially between general medical and care of the elderly departments. In addition, the chairman was not local to the area of the meeting and therefore not an influence on attendees for the region.

The invitations were sent directly from Glaxo Wellcome to all listed general physicians treating epilepsy. The workshop was set up to be interactive, including syndicate sessions. The number of invitations mailed was 113. This was out of 400 general physicians in total (treating all specialities) on the electronic database. Of these invitations, eleven general physicians had accepted to attend the meeting on 27 June. From experience with previous meetings, a few more clinicians might decide to attend the meeting, bringing the expected total of attendees to fourteen. Due to its limited contact with general physicians to date, this was an accurate reflection of the number of positive responses to the invitation the company expected to generate.

Glaxo Wellcome stated that it currently ran fifty meeting each year in epilepsy. Of these fifty meetings, which involved key customers (neurologists, learning disability specialists and paediatricians), only these twelve meetings had been set up as workshops with an honorarium paid for the attendees' time and participation. The reason for this was as previously stated, that it wished to understand the current level of thinking on epilepsy treatment in a new and diverse customer group.

Glaxo Wellcome stated that the invitation sent to the consultant physicians was for an 'Epilepsy Workshop'. The word *workshop*, as opposed to meeting, was clearly used within the letter. The invitation stated that at the workshop the company would share the latest information about anti-

epileptic drugs, the management of epilepsy and *hear the attendees' thoughts* regarding the unmet needs of general physicians treating patients with epilepsy. It also stated that *syndicate sessions* would be employed to discuss issues in the management of women with epilepsy. Within the invitation letter, it was also stated that the invitees would be expected to do *some preparatory work* and that the honorarium of £150 would be paid for the time and participation. Enclosed with the invitation letter, was a fax-back response. This form was also used to capture, in advance of the meeting, the number of patients with epilepsy seen each month by the general physician.

Glaxo Wellcome submitted that within the initial invitation, it was clearly expressed that the invitee would be required to perform some work both prior to and at the workshop and that the honorarium was paid for their time and participation. The company did not accept that the letter of invitation suggested in any way that this was a non-interactive meeting, with the honorarium as an inducement to attend to hear a promotional presentation, and hence an inducement to prescribe.

Two weeks prior to the workshop, each invitee who requested to attend the workshop received a second letter. The purpose of this letter was to reconfirm their attendance at the workshop and to include an agenda for the meeting, the questions to be considered in the syndicate sessions and a copy of each of two publications as pre-reading to provide useful background information for the meeting. A form for claiming travel expenses was also enclosed.

Additional information was sent to the chair of the meeting, which included a copy of the syndicate workshop.

The workshop on 27 June was due to start at 19.15 with a welcome from the chairman. The chairman would then give a presentation of 40 minutes on an update of anti-epileptic drugs (AEDs). This presentation was non-promotional and had been written by the chairman, although for the purpose of this meeting it had been subject to internal approval in accordance with the requirements of the Code and relevant advertising regulations. The presentation covered epilepsy epidemiology, the burden of illness and reviewed the advantages and disadvantages of all AED therapies, including carbamazepine, oxcarbazepine, sodium valproate, vigabatrin, lamotrigine, topiramate, gabapentin, tiagabine, levetiracetam, phenobarbitone, phenytoin and primidone. In addition it also highlighted medicines in development with other pharmaceutical companies, such as remacemide and rufinamide. This presentation was used as stated in the agenda, to update the attendees on the current understanding of AED therapy options.

Following the presentation the attendees were to be divided into syndicate groups, which might be two or three in number to ensure that groups were small enough to allow full participation and discussion. The chairman decided the number of syndicate groups. He/she also nominated the roles within each syndicate of group facilitator, rapporteur and scribe. A workbook was provided which contained seven questions for consideration in discussion on the provided case profile, the workshop reformed with each rapporteur feeding back to the group their conclusions for further discussion within the larger group.

The workshop would be attended by one Glaxo Wellcome representative who was there to observe only. The representative would not be included in the syndicate groups.

The completed workbooks were returned to Glaxo Wellcome. Once the series of meeting was completed, it was planned that the results would be compiled by an external agency with a written report, which would then be sent to all workshop attendees. The report would also be used internally within Glaxo Wellcome to devise an appropriate promotional strategy for seeing general physicians.

The total cost of the meeting on 27 June was £3242.50. This included £175.00 for equipment hire at the venue, £292.50 for food, £75.00 for drinks, honoraria of £150 for fourteen attendees and an honorarium of £400 for the chairman and approximately £200 for travel expenses. The total cost of food and drinks was within a level which individuals might pay for themselves (£24.50). The payment of an honorarium of £150 had previously been ruled as being of an acceptable level in previous cases supplied to Glaxo Wellcome for information.

Glaxo Wellcome did not believe that the workshop was in breach of Clauses 19 or 18.1 of the Code as the invitation letter clearly indicated that the clinician was required to participate in a full and active discussion at the meeting, through use of the syndicate sessions. The honorarium offered was appropriate payment for time and participation born at the meeting and in the required pre work. The presentation was non-promotional on the treatment options available for managing patients with epilepsy. No promotional claims were made for Lamictal and as such the workshop did not constitute an inducement to prescribe. This series of workshops had been devised to gain an understanding of the level of thinking regarding the management of epilepsy by general physicians and to evaluate any regional differences that might exist. The outputs of the meetings were then due to be compiled into a report which would then advise the company on future promotional strategy in this new but important clinician group managing patients with epilepsy.

PANEL RULING

The Panel accepted that there was a difference between holding a meeting for health professionals and employing health professionals to act as consultants to a company. The selection of consultants should stand up to independent scrutiny.

The Panel noted that there had been a number of relevant previous cases. Case AUTH/471/10/96 involved a single focus group meeting. On that occasion the Panel had had some concerns about the meeting. It noted that those attending the meeting had been invited to act as consultants to the company and the number of delegates had been limited thus

ensuring that all could make a contribution to the proceedings. On balance an honorarium of £200 had not been unreasonable for the amount of work involved. The hospitality had been acceptable. No breach of the Code had been ruled. A subsequent case (Case AUTH/686/3/98) concerned ten similar meetings in various locations around the UK. An honorarium of £200 had been offered. In the Panel's view it was questionable whether the attendees would have truly acted as consultants each giving advice to justify such an honorarium and reimbursement of travel expenses. There had not been sufficient justification regarding regional variations in the management of the condition at issue to support the number of meetings held. A breach of Clause 18.1 of the Code had been ruled. This had been upheld on appeal to the Appeal Board which had noted that places were allocated on a first come, first served basis. In the Appeal Board's view there had not been sufficient targeting of the invitations. Another previous case (Case AUTH/944/10/99) concerned one of a series of seven meetings for which the attendees would receive an honorarium of £350. The Panel accepted that there was sufficient clinical justification for the number of meetings held. The chairperson had been chosen by the sponsoring company but the delegates had been chosen by the chairperson. The Panel had some concerns about the meeting but decided on balance that the company was employing health professionals to act as consultants and in that regard the Panel accepted that the honorarium was a genuine payment for advice, Although on the borderline it was not unreasonable for the amount of work involved. No breach of the Code had been ruled in that regard. A breach had been ruled in that case as the letter of invitation made no mention that the recipient was being invited to act as a consultant.

Turning to the case now before it, the Panel noted that the purpose of the workshop was to '…share the latest information about antiepileptic drugs, the management of epilepsy and hear [the invitee's] thoughts regarding the unmet needs of general physicians treating patients with epilepsy'.

The Panel noted that twelve workshops had been held at various locations in England and Scotland. The company had written to invite 113 general physicians. Eleven had accepted to attend the meeting in question. In the Panel's view it was questionable whether all the attendees would have truly acted as consultants to the company each giving such advice as to justify a £150 honorarium and reimbursement of travel expenses.

The Panel considered that it was not unacceptable for companies to pay healthcare professionals and others for advice as to how products should be promoted. It was a question of deciding where the boundary lay. The Panel noted the reasons submitted by Glaxo Wellcome for the need to investigate the management of epilepsy by general physicians and for investigating the regional differences and the effect that these had on patient management. The Panel was however concerned about the overall arrangements for the meetings including the number of meetings and the fact that places were allocated on a first come, first served basis. The invitation was not clear about the expected role of participants.

The Panel noted that the participants were asked to undertake some pre reading. The meeting itself lasted just less than two hours. During that time the participants listened to the chairman's update for 30 minutes, this was followed by 45 minutes of syndicate work. The discussion, summary, conclusion and dinner were allocated a total of 30 minutes.

The Panel considered that overall the meeting constituted a promotional meeting. Reference was made to a number of treatments including Glaxo Wellcome's product. It was not appropriate to pay doctors to attend such meetings. The Panel considered that the only relevant clause in the Code was Clause 18.1. The Panel therefore ruled a breach of Clause 18.1.

Complaint received **16 June 2000**

Case completed **25 July 2000**

CASE AUTH/1042/6/00

DIRECTOR/PARAGRAPH 16 v BOEHRINGER INGELHEIM

Teapot and teacup offer

During its consideration of Case AUTH/1019/4/00 concerning the promotion of Micardis by Boehringer Ingelheim, the Panel noted that a brochure included an offer of a 'Tea for One' teapot and teacup set. The teapot and teacup were of similar size and the teapot was designed such that it sat upon the cup and accompanying saucer. The Panel queried whether the teapot and teacup met the requirements of the Code in that they should be relevant to the recipient's profession and cost less than £5 excluding VAT and decided that the matter should be taken up under Paragraph 16 of the Constitution and Procedure for the Authority.

Following receipt of Boehringer Ingelheim's response, the Panel noted that the cost per set was £4.49 excluding VAT and therefore came within the limit on cost which applied to promotional aids. On balance the Panel did not, however, consider that a gift of a teapot and teacup set was sufficiently relevant to the practice of medicine, notwithstanding the precedent of a coffee mug being allowed. Mugs were single component items, commonplace in almost all workplaces whereas, in the Panel's view, teapot and teacup sets were more of a novelty. The Panel considered that the set was more likely to be taken home by the recipient than used at the surgery. A breach of the Code was ruled.

During its consideration of Case AUTH/1019/4/00 concerning the promotion of Micardis by Boehringer Ingelheim Limited, the Panel noted that a brochure included an offer of a 'Tea for One' teapot and teacup set which had been specifically commissioned from Whittards. The teapot and teacup were of similar size and the teapot was designed such that it sat upon the cup and accompanying saucer.

COMPLAINT

The Panel queried whether the teapot and teacup set met the requirements of Clause 18.2 of the Code and its supplementary information that promotional aids cost the company no more than £5 excluding VAT and that the item had to be relevant to the recipient's profession. The Panel noted that a coffee mug was an acceptable promotional aid provided that it cost no more than £5 excluding VAT but considered that providing a teapot and teacup was not necessarily appropriate. The Panel had asked that the matter be taken up with Boehringer Ingelheim in accordance with Paragraph 16 of the Constitution and Procedure for the Authority.

RESPONSE

Boehringer Ingelheim stated that, in choosing to use this promotional item, it believed it was following accepted standard practice, in that the teapot was integral to the teacup and that coffee mugs were considered acceptable promotional aids. The use of branded cafetières as promotional items was also accepted common practice (Boehringer Ingelheim was aware of four examples by different companies). The item was intended and designed for making a single cup of tea in the workplace environment and cost £4.49 and therefore Boehringer Ingelheim believed that it should be acceptable under Clause 18.2 of the Code.

PANEL RULING

The Panel noted that a copy invoice provided by Boehringer Ingelheim confirmed that the cost per set was £4.49 excluding VAT. It therefore came within the limit of £5 excluding VAT which applied to promotional aids. On balance the Panel did not, however, consider that a gift of a teapot and teacup set was sufficiently relevant to the practice of medicine, notwithstanding the precedent of a coffee mug. The set in question was a limited edition. Mugs were single component items, commonplace in almost all workplaces whereas, in the Panel's view, teapot and teacup sets were more of a novelty. The Panel considered that the set provided by Boehringer Ingelheim was more likely to be taken home by the recipient than used at the surgery. The Panel noted Boehringer Ingelheim's reference to branded cafetières but the acceptability or otherwise of such items had never been the subject of a complaint. The Panel ruled that the gift of the teapot and teacup set, by not meeting the provisions of Clause 18.2, was in breach of Clause 18.1 of the Code.

Proceedings commenced 2 June 2000

Case completed 11 July 2000

CASE AUTH/1044/6/00

BRISTOL-MYERS SQUIBB v AVENTIS PHARMA

Press releases referring to Taxol and Taxotere

Bristol-Myers Squibb complained about two press releases issued by Aventis Pharma. The first press release (issued 16 June) referred to Aventis' product Taxotere (docetaxel) and to guidance issued by the National Institute for Clinical Excellence (NICE) in relation to the treatment of advanced breast cancer. The second press release (issued 21 June) referred to Taxotere and to Bristol-Myers Squibb's product Taxol (paclitaxel).

It was alleged that the second paragraph of the first press release was not substantiable, in particular the statement '… that Taxotere is the most effective treatment to stop the progression of breast cancer and more importantly improve survival'. The claim that Taxotere was the most effective treatment to stop the progression of breast cancer was a superlative and incapable of substantiation. The claim that Taxotere was the most effective treatment to improve survival was also not substantiable. Bristol-Myers Squibb alleged that the second press release, which referred to the first press release, was also in breach. Attention was drawn to the claim '… the Guidance which illustrates that Taxotere has an almost two fold increase in the median progression free survival rates compared with Taxol.' Aventis had admitted that no direct comparative trials had been conducted and the fact that the claim had been restated constituted a further breach. In the first press release, Aventis had claimed 'The Guidance has clearly shown that Taxotere is the most effective treatment to stop the progression of breast cancer and more importantly improve survival'. Bristol-Myers Squibb said it would be seen from the final guidance issued by NICE on the use of taxanes in advanced breast cancer, a copy of which was provided, that no such statement was made. A further breach was alleged. In addition, the second press release claimed 'The basis for this statement is the data recorded in the Guidance which illustrates that Taxotere has an almost two fold increase in the median progression free survival rates compared with Taxol'. As would be seen from final guidance from NICE, there was no such statement and therefore this was also in breach. Bristol-Myers Squibb said that furthermore, as these statements were contained in press releases intended for distribution indirectly to the public, and since they were not factual and might raise unfounded hopes of successful treatment, they were also in breach in that regard.

The Panel noted that there was no one study comparing both products. The Panel considered that the statement in the first Aventis press release '… that Taxotere is the most effective treatment to stop the progression of breast cancer and more importantly improve survival' was misleading. There was no comparative data for Taxotere and Taxol. The statement at issue was more than a comparison between Taxotere and Taxol. It also included the superlative 'most' which was unacceptable. Breaches of the Code were ruled. With regard to the statement '… the Guidance which illustrates that Taxotere has an almost twofold increase in the median progression free survival rates compared with Taxol', the Panel noted Aventis' submission that in a previous case the Code of Practice Appeal Board had accepted that non-directly comparative material might be used to inform healthcare professionals and policy makers about the merits of products in complex areas of treatment like cancer. The Panel noted that the Appeal Board's view was not quite as described by Aventis. The Appeal Board had considered that the use of non-comparative data might be acceptable in certain circumstances, relevant factors being the intended audience, how the data was presented and the conclusions drawn. That case involved a booklet used with oncology specialists. In the Panel's view a press release was a very different document to one that was limited to specialists in the field. The Panel considered that the statement was misleading and a breach of the Code was ruled.

The Panel did not consider that the statement 'The Guidance has clearly shown that Taxotere is the most effective treatment to stop the progression of breast cancer and more importantly improve survival' would be seen as a direct quotation from the guidance. On those narrow grounds no breach of the Code was ruled. Similarly the Panel did not consider that the statement 'The basis for this statement is the data recorded in the Guidance which illustrates that Taxotere has an almost two-fold increase in the median progression free survival rates compared with Taxol' would be seen as a direct quotation from the actual guidance and no breach of the Code was ruled.

The Panel then considered the allegation that the statements were in breach as they were contained in press releases intended for distribution indirectly to the public and they were not factual and might raise unfounded hopes of successful treatment. The Panel considered that the part of the allegation relating to the statement not being factual was covered by its ruling above. The Panel did not consider that the press releases would raise unfounded hopes of successful treatment and no breach of the Code was ruled in that regard.

Bristol-Myers Squibb Pharmaceuticals Limited complained about two press releases issued by Aventis Pharma Ltd. The first press release (issued on 16 June) referred to Aventis' product Taxotere (docetaxel) and to guidance issued by the National Institute for Clinical Excellence (NICE) in relation to the treatment of advanced breast cancer. The second press release (issued 21 June) referred to Taxotere and to Bristol-Myers Squibb's product Taxol (paclitaxel).

Aventis stated that journalists were contacted firstly by telephone and then provided with the press statement by fax. The publications contacted included the lay media (newspapers, BBC radio and television, Sky, Channel 4, IRN etc) and professional publications (BMJ, Pulse, Doctor etc).

COMPLAINT

Bristol-Myers Squibb alleged that the second paragraph of the first press release was not substantiable, in particular the statement:

'… that Taxotere is the most effective treatment to stop the progression of breast cancer and more importantly improve survival'.

The claim that Taxotere was the most effective treatment to stop the progression of breast cancer was a superlative and incapable of substantiation, breaching Clauses 7.2, 7.3 and 7.8. The claim that Taxotere was the most effective treatment to improve survival was also not substantiable, breaching Clauses 7.2, 7.3 and 7.8 of the Code.

Bristol-Myers Squibb stated that in a second press release Aventis Pharma referred to the first press release and attempted to correct the breaches contained in the first press statement. However, the second press release was also in breach; in the third paragraph there was a claim:

'… the Guidance which illustrates that Taxotere has an almost two fold increase in the median progression free survival rates compared with Taxol.'

Aventis had admitted that no direct comparative trials had been conducted and the fact that the claim had been restated and not sufficiently retracted within the wording of paragraph three, constituted a second breach of Clauses 7.2 and 7.3.

Bristol-Myers Squibb stated that in the first press release, Aventis had claimed:

'The Guidance has clearly shown that Taxotere is the most effective treatment to stop the progression of breast cancer and more importantly improve survival'.

It would be seen from the final Guidance issued by NICE on the use of taxanes in advanced breast cancer, a copy of which was provided, that the Guidance made no such statement, therefore this reference to the Guidance was also in breach of Clause 7.2. In addition, in the third paragraph of the second press release Aventis claimed:

'The basis for this statement is the data recorded in the Guidance which illustrates that Taxotere has an almost two fold increase in the median progression free survival rates compared with Taxol'.

As would be seen from final Guidance from NICE, there was no such statement in the Guidance, therefore this statement was also in breach of Clause 7.2.

Furthermore, as these statements were contained in press releases intended for distribution indirectly to the public, and since they were not factual and might raise unfounded hopes of successful treatment, they were in breach of Clause 20.2.

RESPONSE

Aventis Pharma stated that it was the licence holder for Taxotere and had a co-promotional arrangement with Chugai Pharmaceuticals Limited. That being said, Chugai had no part in the development and subsequent management of the Taxotere submission to NICE or with the subsequent press releases concerning the publication of the Institute's Guidance.

In accordance with the supplementary information for Clause 14.1 of the Code, Aventis was the sole defendant in this complaint.

Aventis provided some background to the complaint.

Aventis stated that the Authority would be aware that the taxanes, Taxotere and Taxol, had been the subject of an important assessment by NICE. Following a leak to the BBC and the subsequent television and radio news bulletins on the subject, it was now common knowledge that in the first draft of the Guidance relating to the use of taxanes in breast cancer, the Institute did not recommend the Bristol-Myers Squibb taxane, Taxol, for the treatment of advanced breast cancer. Instead, the Institute limited its Guidance to Taxotere alone. Bristol-Myers Squibb appealed this Guidance and the Institute subsequently modified its Guidance to include Taxol.

It was important for the Authority to keep the following in mind when judging the facts of this complaint. The most senior executives of NICE had stated on several occasions that the Institute's Guidance was intended to establish whether a product or technology was appropriate for use by the NHS in the settings described in the Guidance. The Guidance was not intended to provide a relative ranking between products and technologies unless there were marked differences between products in terms of either their clinical effectiveness or cost effectiveness.

Aventis appealed against the second draft of the Institute's Guidance. Its appeal was made on several points. However, Aventis' appeal concerning the incomplete provision of information by the Institute in its second draft Guidance appeared central to the complaint.

In Section 3.3 of the Guidance the Institute considered that there were four important dimensions for assessing the clinical effectiveness of taxanes. These being response rate, progression free survival, overall length of survival, and quality of life, including toxicity and other serious events.

In Section 1.2.1 of the Guidance the Institute only made mention of two of these four dimensions and Aventis was confused why it had done this when data had been provided to the Institute for all these criteria but the Guidance did not refer to either response rate or overall length of survival.

In brief, during Aventis' appeal to the Institute the Deputy Chairman of the Appraisal Committee reported that the Appraisal Committee believed that median progression free survival subsumed response rate. Interestingly, the NICE Appeal Panel Chairman could not recall a clinical oncology paper that did not refer to response rate in the results section. Aventis then posed the question why oncologists bothered to collect this data if it was not useful. Regrettably, no answer of substance was forthcoming from the Appraisal Committee membership present.

In addition, during the appeal hearing Aventis also challenged why the Institute had included reference to the differences between the two taxanes if material decisions about relative effectiveness could not be made from the data submitted, or the data were not of

sufficient magnitude to be relevant in the terms of the Guidance. The Deputy Chairman of the Appraisal Committee responded by saying that the Committee had considered all of the data and that its Final Assessment Document (the subsequent Guidance from the Institute used exactly the same words) represented the most appropriate information to present so that informed decisions could be made. From this Aventis concluded that the Appraisal Committee thought that there were differences between the two taxanes. However, because a direct comparison had not been made between the two products within the same clinical trial setting this could not be expressed as fact. Moreover though, the Appraisal Committee, and subsequently the Institute, must believe that these data differences for the two products were of sufficient credibility and importance that the readership of the Guidance should be made aware of the data. If this was not the case it was extremely difficult to understand why the Guidance included numerically comparative data and not, as one would expect if the data did not add important additional information, a simple statement limited to comment that both taxanes were considered appropriate for use in accordance with their licensed indications.

Of critical importance to the complaint was the fact that the NICE Appeal Panel was not mindful to request the Appraisal Committee to review the matter again and consider removing the numerically superior progression free survival rates for Taxotere compared with Taxol.

Aventis' appeal failed to convince the Institute to increase the comparative data included in the Guidance to include all four critical evaluation dimensions identified by the Institute in its own document (published Guidance, Section 3.3). Aventis also failed to convince the Institute to exclude the comparative data included in the Guidance.

Aventis believed that the only reasonable conclusion that could be drawn from the failure of its appeal was that the Appeal Panel considered that the Appraisal Committee had not produced a flawed appraisal of the data and that the Institute's Guidance was appropriate to publish in a form that presented data showing numerical superiority of one product compared with another.

Aventis' public relations director received a telephone call from the press officer of Bristol-Myers Squibb on Friday, 18 June. Bristol-Myers Squibb asked Aventis for a copy of its press release and offered to share a copy of its own press release with Aventis. Aventis' press release was faxed to Bristol-Myers Squibb that evening.

The next working day, Aventis' medical director received a fax from his counterpart at Bristol-Myers Squibb pointing out some concerns that Bristol-Myers Squibb had with Aventis' press release. As would be seen from the copy provided, Bristol-Myers Squibb requested a repeat press release correcting what it saw as errors in the communiqué. It was mentioned that if Aventis failed to provide this Bristol-Myers Squibb would take the matter up with the Authority.

After careful reflection Aventis considered that the possibility that an ambiguity might exist in the minds of some readers of its first release could not be excluded and, rather than confuse anyone, Aventis believed that it would be clearer to issue a second communiqué which was sent to Bristol-Myers Squibb.

Aventis was not aware of any published clinical trial directly comparing Taxotere to Taxol. This being said, Aventis did not believe that such a trial had to have been performed in order that informed intelligent conclusions could be drawn. This was the same view and approach that the regulators of licensed medicines frequently took when they accepted 'bridging' data between compounds, formulations and devices. Notwithstanding this, Aventis did believe that readers should be made aware of the type and quality of the available data. Aventis' belief in this second point was the reason it decided to issue a second release that made the types of data crystal clear.

With regard to substantiation of the statement '… that Taxotere is the most effective treatment to stop the progression of breast cancer and more importantly improve survival …', Aventis referred to Section 1.2.1 of the Guidance. This drew attention to the fact that there was twice the volume of clinical evidence to support the submission of Taxotere (4 randomised controlled trials (RCTs) and approximately 1000 patients) compared with Taxol (2 RCTs and approximately 500 patients) and that different comparator drugs were used in these controlled trials.

In the same section the Institute's Guidance went on to make statements about the increase in median progression free survival over the control treatment. Importantly though, the Guidance failed to inform the clinician what the controls were so that an assessment of the incremental benefit could be made and thereby provide an environment for informed decision making with the patient about which treatment to choose.

Aventis sought to improve the Guidance by taking the matter of data type clarity to appeal because the Institute's guidance did not include such clarification. As the appeal was not upheld, it was clear that the Appeal Panel did not believe it was necessary to provide this type of information for informed decision making. As a result of this judgement and to keep in line with the Institute, Aventis did not expand upon this point in its first press release, instead relying on the Institute's own approach. However, following the concerns Aventis received from Bristol-Myers Squibb, Aventis decided to clarify the matter in its second press release.

In contrast to the Taxotere data, the two RCTs supporting the Taxol submission were conducted and either published or submitted for publication prior to 1995. The comparator treatments in these two Taxol supporting RCTs were single agent mitomycin (12mg/m^2 bolus every six weeks) Phase II, and an unlicensed, sub-optimal dose of paclitaxel (135mg/m^2) Phase III.

It was important to note that the comparators used in the Taxotere studies were, by general consent amongst oncologists specialising in this area, considered to be superior to the comparators used in the Taxol studies. The comparators in the Taxotere studies were

doxorubicin Phase III, mitomycin and vinblastine Phase III, sequential methotrexate and 5-fluoruracil Phase III, and vinoralbine and 5-fluoruracil Phase III.

For example, the study comparing Taxotere to a mitomycin containing regimen (12mg/m^2 bolus every six weeks) also contained vinblastine (6mg/m^2 every three weeks). Professor Nabholtz, the author of the Taxotere paper published in the Journal of Clinical Oncology in 1999 reporting the Taxotere vs vinblastine and mitomycin study, was the same investigator that performed the 1995 Taxol vs mitomycin trial. Professor Nabholtz specifically included a statement in his 1999 paper for Taxotere that 'Several reports have shown that MV (mitomycin, vinblastine) has a greater tumour activity than either agent alone'.

Aventis stated that it was clear from the following published randomised clinical trial results that formed the critical parts of the clinical efficacy data submissions to the Institute that there were very important differences between the two compounds. In all but one of the dimensions (overall survival) the lowest efficacy rate for Taxotere was superior to the highest value observed for Taxol.

Response rate	Taxotere 30-48%	Taxol 17-29%
Progression free survival	Taxotere 19 weeks – 6.3 months	Taxol 3.5 – 4.2 months
Overall survival	Taxotere 11.4 – 15 months	Taxol 11.7 months

With regard to whether meaningful conclusions could be drawn from non-directly comparative trials, Aventis submitted that it was standard practice in the treatment of cancer that clinical decisions were made based on clinical studies that were not direct comparisons between agents. In this complex area clinicians were highly trained and able to interpret the strengths and shortcomings of such data. Moreover, the Code of Practice Appeal Board, in a recent ruling in Cases AUTH/824/1/99 and AUTH/825/1/00, concluded that non-directly comparative data might be used to inform doctors and healthcare professionals and policy makers about the merits of products in complex areas of treatment like cancer.

As a result of the quality of the trials and the nature of the results of the above trials, Aventis believed that its press release could be substantiated and that it did not represent a breach of the Code.

Aventis referred to Bristol-Myers Squibb view that Aventis' statement was in breach of the Code as there was no such statement in the Guidance.

By making this allegation Bristol-Myers Squibb implied that Aventis had taken a quotation from the guidance. It had not. As Aventis stated in its second press release: 'The basis for this statement is the data recorded in the Guidance which illustrates that Taxotere has an almost two-fold increase in the median progression free survival rates compared with Taxol.'

This data was clearly written in the Guidance in Section 1.2.1. As a result Aventis did not believe that these two alleged breaches of Clause 7.2 had substance.

As set out above, all statements in Aventis' press release concerning the Guidance issued by the Institute had been factual and presented in a balanced way. Aventis believed that its press release had neither raised unfounded hope, nor was it misleading with respect to the safety of the product. In addition Aventis did not believe that its press release encouraged members of the public to ask their doctors to prescribe a specific medicine. Accordingly Aventis rejected the allegation that its press release was in breach of Clause 20.2.

PANEL RULING

The Panel noted Aventis' submission that the first draft Guidance on the use of Taxanes for Breast Cancer did not recommend Bristol-Myers Squibb's product for the treatment of advanced breast cancer. Bristol-Myers Squibb appealed and the Guidance was modified to include Taxol. Aventis appealed against the second draft of the Guidance. The Panel also noted that there was no one study comparing both products.

The Panel considered that the statement in the first Aventis press release '… that Taxotere is the most effective treatment to stop the progression of breast cancer and more importantly improve survival' was misleading. There was no comparative data for Taxotere and Taxol. The statement at issue was more than a comparison between Taxotere and Taxol. The statement also included a superlative 'most'. A superlative could only be used in relation to a simple statement of fact which could be very clearly demonstrated. The Panel considered that the use of the superlative 'most' was unacceptable. The Panel ruled breaches of Clauses 7.2 and 7.8. The Panel considered that the alleged breach of Clause 7.3 was covered by these rulings.

With regard to the statement '… the Guidance which illustrates that Taxotere has an almost twofold increase in the median progression free survival rates compared with Taxol', the Panel noted Aventis' submission that the Appeal Board had accepted that non-directly comparative material might be used to inform doctors and healthcare professionals and policy makers about the merits of products in complex areas of treatment like cancer. The Panel noted that the Appeal Board's view was not quite as described by Aventis. The Appeal Board had considered that the use of non-comparative data might be acceptable in certain circumstances, relevant factors being the intended audience, how the data was presented and the conclusions drawn. That case involved a booklet used with oncology specialists. In the Panel's view a press release was a very different document to one that was limited to specialists in the field. The Panel considered that the statement was misleading. A breach of Clause 7.2 was ruled. The Panel considered that the alleged breach of Clause 7.3 was covered by its ruling of a breach of Clause 7.2.

The Panel did not consider that the statement 'The Guidance has clearly shown that Taxotere is the most effective treatment to stop the progression of breast cancer and more importantly improve survival' would be seen as a direct quotation from the

Guidance. On those narrow grounds no breach of Clause 7.2 of the Code was ruled. Similarly the Panel did not consider that the statement 'The basis for this statement is the data recorded in the Guidance which illustrates that Taxotere has an almost two-fold increase in the median progression free survival rates compared with Taxol' would be seen as a direct quotation from the actual Guidance. On those narrow grounds no breach of Clause 7.2 of the Code was ruled.

The Panel then considered the allegation that as the statements were contained in press releases intended for distribution indirectly to the public and since they were not factual and might raise unfounded hopes of successful treatment, they were in breach of Clause 20.2. The Panel considered that the part of the allegation relating to the statement not being factual was covered by its ruling of breaches of Clauses 7.2 and 7.3 above. The Panel did not consider that the press releases would raise unfounded hopes of successful treatment and no breach of Clause 20.2 was ruled in this regard.

Complaint received **26 June 2000**

Case completed **9 August 2000**

CASE AUTH/1045/7/00 *NO BREACH OF THE CODE*

CONSULTANT IN PUBLIC HEALTH MEDICINE v SCHERING-PLOUGH

Supply of Remicade

A consultant in public health medicine/medical adviser to a health authority complained about the supply of infliximab (Schering-Plough's product Remicade) to a local rheumatology consultant to treat patients with arthritis. The complainant's understanding was that Remicade was not licensed and he had been told it was supplied free of charge. There had been some consternation among patients as they had then been told that it had been stopped because it was not being funded. It was only after this that the local rheumatologist had put together a business case and started to take it through the appropriate channels for consideration for funding. The complainant's concern was that if Remicade was supplied free of charge to the consultant then it might be a form of promotion prior to it being licensed so as to encourage it to be continued through NHS funding after it had been licensed. In other words this might be seen as a form of disguised promotion.

The Panel noted that Remicade had been licensed for the treatment of Crohn's disease since August 1999 and had received a licence for rheumatoid arthritis on 21 June 2000. Prior to the amendment of its licence in this regard, whilst Remicade could not be promoted for rheumatoid arthritis, the provision of Remicade on a named patient basis for compassionate use in response to a *bona fide* unsolicited request from a physician was not necessarily unacceptable. Such provision would only be covered by the Code if the overall arrangements were promotional.

The Panel noted Schering-Plough's submission regarding the publicity generated when results of clinical trials were published and the requests it had received from rheumatologists for the supply of the product on a compassionate use basis. The Panel noted that the rheumatologist referred to by the complainant had participated in clinical trials for rheumatoid arthritis. The Panel examined the request forms completed by the rheumatologist.

The Panel noted the concerns of the complainant but considered there was no evidence that overall the arrangements for the provision of Remicade had been promotional. The Panel did not consider that the circumstances constituted promotion of an unlicensed medicine or an unlicensed indication and ruled no breach of the Code. The Panel did not accept that the supply amounted to a form of disguised promotion and ruled no breach of the Code in that regard either.

COMPLAINT

A consultant in public health/medical adviser to a health authority alleged that there had been some difficulties about the use of infliximab (Schering-Plough Ltd's product, Remicade) in his local trust. It would appear that a rheumatology consultant in the trust had used it to treat a patient with arthritis. The complainant's understanding was that Remicade was not licensed and he had been told it was supplied free of charge to the rheumatologist to give to patients.

There had been some consternation among several patients as they had then been told that it had been stopped because it was not being funded. This had involved letters being written to MPs. It was only after this that the local rheumatologist had put together a business case and started to take it through the appropriate channels of the local trust and the health authority if appropriate for consideration for funding.

The complainant's concern was that if Remicade was supplied free of charge to the consultant for a patient then it might be a form of promotion prior to it being licensed so as to encourage it to be continued through NHS funding after it had been licensed. In other words this might be seen as a form of disguised promotion.

RESPONSE

Schering-Plough stated that Remicade, now licensed for rheumatoid arthritis, was the object of significant attention when the results of its clinical trials in rheumatoid arthritis were released last year. Several UK sites were involved in these trials.

Schering-Plough received a significant number of requests from rheumatologists for Remicade on a compassionate use basis for treating patients with severe rheumatoid arthritis, who had failed or were intolerant to other medications. In response to these requests Schering-Plough agreed to make available a named patient supply of Remicade in response to direct requests from physicians.

It was made clear in a memorandum, sent only in response to queries from interested physicians, that the company would be prepared to supply Remicade to suitable patients, on a named patient basis, free of charge, up to the time the product was launched and commercially available.

The Medicines Control Agency (MCA) was notified of Schering-Plough's wish to import for named patient use, in accordance with the Medicines (Exemption from Licences) (Importation) Order 1984 (SI 1984 no 673), and it replied to state that: 'The exemption conferred by Article 3 of the Order will take effect'. In line with the requirements of SI 1984 No 673 Schering-Plough committed to the MCA to provide product only in response to *bona fide* unsolicited orders, to maintain adequate records of quantities imported and the names or initials of patients receiving treatment and document the maximum number of product which could be imported.

Schering-Plough stated that Remicade was supplied, free of charge, for named patients, for whom the consultant in question requested a supply. An examination of Schering-Plough's files revealed that this consultant received Remicade for six patients. Schering-Plough would be pleased to share, in confidence, the requests from the physician and, in the meantime, provided an example of the form which all doctors requesting Remicade were requested to complete before their application could be processed. Schering-Plough had reviewed the files relating to the supply of Remicade for this doctor's patients and could confirm that each patient was the subject of a signed request for supply.

Remicade had been licensed since 21 June in the UK for the reduction of signs and symptoms in patients with rheumatoid arthritis when the response to disease modifying drugs, including methotrexate, had been inadequate. Remicade was presented as a vial of 100mg of powder for concentration for solution for infusion. This was the same presentation used in both the treatment of Crohn's disease and rheumatoid arthritis.

In response to a request for further information Schering-Plough provided copies of the requests from the consultant rheumatologist for supplies of Remicade. His initial request was for the use of a single patient, in May 1999. Subsequent to that he requested named patient supplies of medicines for other patients.

Schering-Plough confirmed that this rheumatologist had participated in registration clinical trials in rheumatoid arthritis, with Schering-Plough products since 1997. In addition to participating in these trials he had been involved in Schering-Plough advisory boards.

Schering-Plough sales representatives were not permitted to mention unlicensed indications, clinical trials or unlicensed products unless spontaneously asked by a doctor. Such requests were passed on to, depending on their nature, the medical information service, the medical affairs department or the medical director.

All representatives underwent training on the Code, and mention was specifically made of the above points in the training. The local representative covering this physician's hospital had taken, and passed, the ABPI Medical Representatives Examination.

The local representative had confirmed that he did not speak to the rheumatologist concerning the availability of Remicade as named patient supplies. From Schering-Plough's records the first request by this doctor for a named patient supply of Remicade was on or before 24 May 1999. The first contact between the physician and the local representative was on 21 October 1999.

In summary, Schering-Plough provided named patient supply of Remicade to a physician who was aware of the data on this product and who requested drug for individual patients who had run out of treatment options. The response to the request was in line with the spirit and rulings of the Code and Medicines Act. The requests and responses were dealt with by the Medical Affairs Division of Schering-Plough. The sales representatives were not involved, and there was no mention, or activity, to promote the product outside its licensed indication.

PANEL RULING

The Panel noted from the summary of product characteristics that Remicade was indicated for, *inter alia*, rheumatoid arthritis; the reduction of signs and symptoms in patients with active disease when the response to disease-modifying drugs, including methotrexate, had been inadequate. Efficacy and safety had been demonstrated only in combination with methotrexate. Remicade had previously been licensed for the treatment of Crohn's disease (August 1999) and had received a licence for rheumatoid arthritis on 21 June 2000.

The Panel noted that prior to the amendment of its licence in this regard, whilst Remicade could not be promoted for rheumatoid arthritis, the provision of Remicade on a named patient basis for compassionate use in response to a *bona fide* unsolicited request from a physician was not necessarily unacceptable. Such provision would only be covered by the Code if the overall arrangements were promotional.

The Panel noted Schering-Plough's submission regarding the publicity generated when results of clinical trials were published and the requests it had received from rheumatologists for the supply of the product on a compassionate use basis. The Panel

noted that the rheumatologist referred to by the complainant had participated in the clinical trials for rheumatoid arthritis and had been involved in Schering-Plough's advisory boards. The Panel examined the request forms completed by the rheumatologist. Remicade had been supplied for six patients who had participated in the clinical trial. At the time of the first request, May 1999, Remicade was not licensed. Other requests were dated after the product was licensed for Crohn's disease but before it was licensed for rheumatoid arthritis.

The Panel noted the concerns of the complainant but considered there was no evidence that overall the arrangements for the provision of Remicade had been promotional. The Panel did not consider that the circumstances constituted promotion of an unlicensed medicine or an unlicensed indication and ruled no breach of Clauses 3.1 and 3.2. The Panel did not accept that the supply amounted to a form of disguised promotion and ruled no breach of Clause 10.1 of the Code.

Complaint received **3 July 2000**

Case completed **29 August 2000**

CASE AUTH/1046/7/00

BRISTOL-MYERS SQUIBB and SANOFI-SYNTHÉLABO v SOLVAY HEALTHCARE

Teveten journal advertisement

Bristol-Myers Squibb and Sanofi-Synthélabo complained jointly about a journal advertisement for Teveten (eprosartan) issued by Solvay Healthcare. Teveten was a nonpeptide angiotensin II receptor antagonist. The advertisement featured an illustration of a goalkeeper with very large gloves defending the goal which appeared above a claim 'Have an unfair advantage over hypertension.' The claim 'Dual action. Single daily dose' appeared beneath the brand name in the bottom right hand corner of the advertisement adjacent to the claim 'Solvay Healthcare's new AII antagonist gives you effective blood pressure control with placebo like tolerability. Who said life's unfair?' The complainants alleged that the claim 'Dual Action' implied directly that eprosartan worked in two distinct ways, namely by action at vascular AT1 receptors and at pre-synaptic AT1 receptors. The evidence to substantiate the claim was entirely animal based. There was no evidence in man that activity at the pre-synaptic AT1 receptor contributed to the antihypertensive effect of eprosartan. The Code stated that extrapolation of animal data to the clinical situation should only be made where there were data to show it was of direct relevance and significance. This claim was alleged to be misleading, incapable of substantiation and ambiguous. It was also alleged to be in breach because the Code required that claims should not imply that a medicine or an active ingredient had some special merit, quality or property unless this could be substantiated. Furthermore, the claim 'Solvay Healthcare's new AII antagonist gives you effective blood pressure control with placebo-like tolerability' together with the claim 'Have an unfair advantage over hypertension' gave the overall impression that effective blood pressure control and placebo-like tolerability were characteristics not shared by other agents in the class. This was alleged to be misleading.

The Panel noted that the claim 'Dual action' was based on data from animal studies which showed that eprosartan worked by action at vascular AT1 receptors and in addition to some other AII antagonists blocked a second subset of AII receptors located pre-synaptically on peripheral sympathetic nerves. The Panel noted Solvay Healthcare's submission that the effect of this action was attenuation of sympathetically mediated increase in peripheral resistance and that this might be relevant to the antihypertensive effect of eprosartan. Teveten's summary of product characteristics described the product as an angiotensin II receptor antagonist which bound selectively to the AT1 receptor. There was no mention of prejunctional AII receptors nor of sympathetic nerve activity.

The Panel did not accept that the claim 'Dual action' was simply a statement of pharmacological action; it would not be read in isolation but would be considered in light of the advertisement as a whole and would be seen as a clinical effect. In the absence of an explanation to the contrary a reader might assume that the dual action was one reason why eprosartan had an unfair advantage over hypertension. The animal studies referred to the fact that the presynaptic action might be relevant to the product's antihypertensive effect. The clinical effect was not known. The Panel considered the claim 'Dual action' in the advertisement misleading in this regard and ruled a breach of the Code. The Panel considered that 'Dual action' in the context of the advertisement implied that Teveten had a special quality and this was not capable of substantiation. A breach of the Code was ruled in that regard also. The Panel did not accept that the claims 'Solvay Healthcare's new AII antagonist gives you effective blood pressure control with placebo-like tolerability' and 'Have an unfair advantage over hypertension' gave the impression that effective blood pressure control and placebo like tolerability were characteristics not shared by other agents in the class. There were no direct or implied comparative claims in this regard. The Panel ruled no breach of the Code in that respect.

Bristol-Myers Squibb Pharmaceuticals Limited and Sanofi-Synthélabo complained jointly about an advertisement for Teveten (eprosartan) issued by Solvay Healthcare Limited which had appeared in GP on 14 April. Teveten was a nonpeptide angiotensin II receptor antagonist.

The advertisement featured an illustration of a goalkeeper with very large gloves defending the goal which appeared above a claim 'Have an unfair advantage over hypertension.' The claim 'Dual action. Single daily dose' appeared beneath the brand name in the bottom right hand corner of the advertisement adjacent to the claim 'Solvay Healthcare's new AII antagonist gives you effective blood pressure control with placebo like tolerability. Who said life's unfair?'

COMPLAINT

Bristol-Myers Squibb and Sanofi-Synthélabo alleged that the claim 'Dual Action', which appeared beneath the product name, implied directly that eprosartan worked in two distinct ways, namely by action at vascular AT1 receptors and at pre-synaptic AT1 receptors. The evidence provided by Solvay Healthcare to substantiate the claim was entirely animal based. There was no evidence in man that activity at the pre-synaptic AT1 receptor contributed to the antihypertensive effect of eprosartan. The claim was alleged to be in breach of Clause 7.2 of the Code which stated that extrapolation of animal data to the clinical situation should only be made where there were data to show it was of direct relevance and significance. This claim was misleading, incapable of substantiation and ambiguous and was therefore in breach of Clauses 7.2 and 7.3 of the Code. It was also in breach of Clause 7.8 which required that claims should not imply that a medicine or an active ingredient had some special merit, quality or property unless this could be substantiated.

Furthermore, the claim 'Solvay Healthcare's new AII antagonist gives you effective blood pressure control with placebo-like tolerability' together with the claim 'Have an unfair advantage over hypertension' gave the overall impression that effective blood pressure control and placebo-like tolerability were characteristics not shared by other agents in the class. This was misleading in breach of Clause 7.2 of the Code.

RESPONSE

Firstly, with regard to the dual mode of action of Teveten, Solvay Healthcare stated that this was based on data from animal studies from several investigators showing that eprosartan blocked angiotensin II (AII) receptors on vascular smooth muscle but additionally, and in contrast, to some other angiotensin II antagonists, blocked a second sub-set AII of receptors located pre-synaptically on peripheral sympathetic nerves. This latter action served to block an AII stimulated amplifier effect leading to increased release of noradrenaline from the sympathetic nerve terminals, the result was attenuation of sympathetically mediated increase in peripheral resistance. This might be relevant to the antihypertensive effect of eprosartan, but no claims were made in this regard. 'Dual mode of action' was simply a statement of established pharmacological action with no attempt to mislead as to its significance or to extrapolate resultant clinical benefits.

Solvay Healthcare submitted that a recent case before the Authority (Case AUTH/796/11/98) relating to a claim for specificity for a selective serotonin re-uptake inhibitor (SSRI) antidepressant might be considered to be relevant in consideration of this point. The claim in question was based entirely on *in vitro* data. Although there was discussion over what this might mean clinically, it was recognised that there was no proven benefit which resulted from this particular pharmacological selectivity; the claim was allowed as a statement of fact. Furthermore, other antidepressants were described by their pharmacological profile (SNRI, NARI, $5HT_2$ – antagonist, noradrenaline/serotonin enhancer, etc) again with no clinical relevance as antidepressant activity had not been shown to be directly related to any of these pharmacological properties. There were many more examples of medicines that were described and promoted according to a mode of action which had not been shown to account for their clinical effects. The supplementary information to Clause 7.2 of the Code made the issue clear and did not prohibit this kind of statement as long as 'care is taken …so as not to mislead as to its significance' and that extrapolation should only be made when it could be shown that it was '…of direct relevance and significance'.

Solvay Healthcare had been very careful to make this a simple statement relating to pharmacological mode of action. It was based on several scientific studies and was justified by the results. There was no extrapolation to possible resultant clinical benefits that could accrue from this pharmacological activity.

Solvay Healthcare considered that the claim for a dual pharmacological action had been substantiated and was not misleading and, therefore, there had been no breach of Clause 7.2 of the Code.

Secondly, in response to the complaint about the advertisement strapline 'Have an unfair advantage over *hypertension*' (Solvay Healthcare's emphasis). This was a clear and unambiguous statement referring to treatment of the disorder. Furthermore, the statement that appeared immediately below it reinforced the meaning: 'Solvay Healthcare's new AII antagonist gives you blood pressure control with placebo-like tolerability. Who said life's unfair?'. Again, this was a simple statement of fact regarding Teveten, with no comparative element. Solvay Healthcare absolutely disagreed with the purported impression of the complainants and maintained that there had been no breach of Clause 7.2.

PANEL RULING

The Panel noted that the claim 'Dual action' was based on data from animal studies which showed that eprosartan worked by action at vascular AT1 receptors and in addition to some other AII antagonists blocked a second subset of AII receptors located pre-synaptically on peripheral sympathetic nerves.

The Panel noted the supplementary information to Clause 7.2 headed 'The use of data derived from *in vitro* studies, studies in healthy volunteers and in animals' which stated that care must be taken with the use of such data so as not to 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 Case AUTH/796/11/98, referred to by Solvay Healthcare, concerned the promotion of Cipramil by Lundbeck. It was alleged that the claim 'Cipramil – the most selective SSRI' was misleading as it was unclear what clinical benefit derived from selectivity. The Panel had noted the product's summary of product characteristics (SPC) which stated that it was the most selective serotonin re-uptake inhibitor yet described with no or minimal effect on noradrenaline, dopamine and gamma aminobutyric acid uptake. The Panel noted data which stated Cipramil was the most selective 5-HT re-uptake inhibitor. The Panel ruled no breach of Clause 7.2. On appeal the Appeal Board considered that given the statement in the SPC and data the claim was not misleading as alleged. Another allegation was made regarding a heading 'Why is selectivity important?' which introduced a section discussing the concept of selectivity with reference to *in vitro* studies. The Panel considered that it was neither stated nor implied that no side effects would occur. The section attempted to explain the scientific theory behind selectivity. No breach of Clause 7.2 was ruled.

Turning to the case now before it, the Panel noted that Ohlstein *et al* (1997), a study in rats, stated that eprosartan was chemically distinct from all other non-peptide AII receptor antagonists in that it was a non-biphenyl non-tetrazole compound. The authors concluded that the data suggested significant differences between the non-peptide AII receptor antagonists eprosartan, losartan, valsartan and irbesartan in their ability to inhibit sympathetic outflow, eprosartan being significantly more effective than the others. This difference might be related to its ability to block prejunctional AII receptors to a greater degree. The study authors stated that it remained to be determined whether this might result in greater efficacy in lowering systolic blood pressure clinically and whether eprosartan was more effective at treating isolated systolic hypertension. Sun *et al* (2000) in an abstract concluded that in a rat model of congestive heart failure eprosartan, *inter alia*, might influence blood pressure regulation by an inhibitory effect at the level of the sympathetic nerve terminal.

The Panel noted the submission that the effect of this action was attenuation of sympathetically mediated increase in peripheral resistance and that this might be relevant to the antihypertensive effect of eprosartan. Teveten's SPC described the product as an angiotensin II receptor antagonist which bound selectively to the AT1 receptor. There was no mention of prejunctional AII receptors nor of sympathetic nerve activity.

The Panel considered that the case now before it was different from the case referred to by Solvay in its response, Case AUTH/796/11/98. In the previous case the SPC stated that Cipramil was the most selective 5-HT re-uptake inhibitor. Antidepressants were often described by their pharmacological profile such as selective serotonin re-uptake inhibitor (SSRI) or selective noradrenaline re-uptake inhibitor (NARI).

The Panel did not accept that the claim 'Dual action' was simply a statement of pharmacological action; it would not be read in isolation but would be considered in light of the advertisement as a whole and would be seen as a clinical effect. The Panel considered that in the absence of an explanation to the contrary a reader might assume that the dual action was one reason why eprosartan had an unfair advantage over hypertension. The animal studies referred to the fact that the presynaptic action might be relevant to the product's antihypertensive effect. The clinical effect was not known. The Panel considered the claim 'Dual action' in the advertisement misleading in this regard and ruled a breach of Clause 7.2 of the Code. The Panel considered that 'Dual action' in the context of the advertisement implied that Teveten had a special quality and this implication was not capable of substantiation. A breach of Clause 7.8 of the Code was ruled. The Panel considered that the alleged breach of Clause 7.3 was covered by its rulings of a breach of Clauses 7.2 and 7.8 of the Code.

The Panel did not accept that the claims 'Solvay Healthcare's new AII antagonist gives you effective blood pressure control with placebo-like tolerability' and 'Have an unfair advantage over hypertension' gave the impression that effective blood pressure control and placebo like tolerability were characteristics not shared by other agents in the class. There were no direct or implied comparative claims in this regard. The Panel ruled no breach of Clause 7.2 of the Code.

During its consideration of this case the Panel noted that the non-proprietary name appeared to be less than 10 point bold as required by Clause 4.1 of the Code. The Panel requested that its concerns were drawn to the attention of Solvay.

Complaint received **4 July 2000**

Case completed **30 August 2000**

GENERAL PRACTITIONER v BAYER

Lipobay leavepiece

A general practitioner complained about a Lipobay leavepiece handed out by Bayer representatives. One side included a thermometer with a visual of a man holding drum beaters and about to hit what could be seen as a gong. Instead of a clear picture of a gong there was a gong shaped fuzzy yellow oval. The centre of the oval was blue in colour. Part of the oval shape was obscured by a thermometer which was positioned in the bottom right hand corner. The complainant stated that he was extremely disgusted at the offensive and totally unnecessary use of a phallic symbol in the middle of the 'gong'. This was placed such that if the thermometer was showing then the phallus was in full view.

The Panel noted the complainant's view and understood his concern. The centre of the oval might be viewed by some as a phallic symbol. Others might see it as the shadow of the man beating the gong. In the Panel's view it was unlikely that the audience would see the illustration as being of an atherosclerotic artery as had been submitted by Bayer. The Panel considered that on balance the illustration would not be likely to cause offence and no breach of the Code was ruled.

A general practitioner complained about the promotion of Lipobay by Bayer plc, Pharmaceutical Division.

The item at issue was a card (ref 9LIPO162) handed out by representatives as a leave piece. It was designed to stand on the desk. One side included a thermometer with a visual of a man holding drum beaters and about to hit what could be seen as a gong. Instead of a clear picture of a gong there was a gong shaped fuzzy yellow oval. The centre of the oval was blue in colour. Part of the oval shape was obscured by the thermometer which was positioned in the bottom right hand corner. The only text on this side of the item related to the thermometer. The other side of the item included some claims for Lipobay. The prescribing information was given on the inside.

COMPLAINT

The complainant stated that he was extremely disgusted at the offensive and totally unnecessary use of a phallic symbol in the middle of the 'gong'. This was placed such that if the thermometer was showing then the phallus was in full view.

The complainant stated that it was totally unnecessary for a pharmaceutical company to use such material in their advertising and hoped that the company would be appropriately reprimanded.

RESPONSE

Bayer stated the reference to the 'gong' was a cross section of an atherosclerotic artery which was used in the promotion of Lipobay in 1999. The company could not see the phallic symbol to which the complainant referred. If the image could be interpreted in this way then there was obviously no intention on the company's part to depict such a representation. Bayer did not see that there was a case to answer. The item at issue had not been distributed since the end of 1999.

PANEL RULING

The Panel noted the complainant's view and understood his concern. The centre of the oval might be viewed by some as a phallic symbol. Others might see it as the shadow of the man beating the gong. In the Panel's view it was unlikely that the audience would see the illustration as being of an atherosclerotic artery. The Panel noted that the item at issue had not been distributed since the end of 1999. The Panel considered that on balance the illustration would not be likely to cause offence and no breach of Clause 9.1 of the Code was ruled.

Following its consideration of this case the Panel was concerned that the prescribing information was inaccessible. The card had to be taken apart in order to read the prescribing information which appeared on the inside. This was not acceptable. The Panel requested that its views be passed on to Bayer.

Complaint received **5 July 2000**

Case completed **21 August 2000**

GENERAL PRACTITIONER v ASTRAZENECA

Oxis Turbohaler 12 'Dear Doctor' letter

A general practitioner complained about a 'Dear Doctor' letter on Oxis Turbohaler 12 (eformoterol) sent by AstraZeneca. The letter was headed 'Give long lasting bronchodilation the green light' and discussed the product's duration of bronchodilation and onset of action.

In relation to the claims 'Oxis Turbohaler 12 may require less use of rescue medication compared with those taking salmeterol…' and 'Oxis Turbohaler 12 has also been shown to deliver significantly greater improvement in lung function 60 minutes after administration with salmeterol 50mcg', the complainant noted that they were both referenced to a poster presented at a congress and to data on file. The complainant did not think that a poster was an adequate vehicle for proof of effect or that such a comparison could be substantiated by 'data on file' only.

The Panel noted that the claims at issue were referenced to a poster and data on file. Such references were not prohibited *per se* under the Code which required each claim to be capable of substantiation and substantiation to be provided on request. The issue therefore was whether each claim could be substantiated by the data provided. In relation to the claim 'a study has shown patients on Oxis Turbohaler 12 may require less use of rescue medication compared with those taking salmeterol breath-activated multi-dose inhalers', the Panel noted that the Sill *et al* (1998) poster stated that the trial was a randomised open study in 102 patients with moderate asthma designed to compare the onset of action of Oxis Turbohaler and salmeterol. The data on file stated that its analysis was additional to those presented in the published paper, abstract and poster. The data on file concluded that the reduction in rescue medication from pre-trial to treatment phase was significantly greater in the Oxis Turbohaler group compared to the salmeterol group. The Panel noted that adjacent to the claim was an asterisk which referred the reader to a footnote at the bottom of the page which read 'compared with baseline'. It was an accepted principle under the Code that a main claim could not be qualified by a footnote. The Panel considered that the claim at issue gave the impression that patients in the Oxis group might have used significantly less rescue medication than patients in the salmeterol group; the data on file, however, analysed the change in use of rescue medication within each patient group and then compared the change in mean number of rescue inhalations per day with Oxis to that with salmeterol. The Panel noted that the salmeterol group started with a lower level of pre-trial rescue medication usage. The term 'may' was used. On balance, the Panel considered that the claim was not misleading and was capable of substantiation. No breach of the Code was ruled.

In relation to the claim 'Oxis 12 Turbohaler has also been shown to deliver significantly greater improvement in lung function 60 minutes after administration compared to salmeterol 50mcg', the Panel noted that Sill *et al* was designed to measure specific airway resistance at prespecified time points; 2, 5, 10, 20 and 60 minutes after inhalation. Additionally FEV_1 was measured at 10, 20 and 60 minutes after inhalation. The poster stated that two minutes after inhalation of one dose of Oxis a medium reduction of 29% in specific airway resistance (SRaw) was observed. 'In contrast there was no change in the Serevent treated group (SRaw =+1%). This difference was of high statistical significance ($p<0.0001$)'. The Panel noted that Figure 1 of the poster, a graph depicting the reduction in SRaw from baseline of salmeterol and Oxis between 0 and 60 minutes, whilst indicating between group difference did not indicate the statistical significance of this difference as no p values were provided. The between group differences appeared to be markedly less at 60 minutes than at 2 minutes. The Panel did not know whether the difference at 60 minutes was statistically significant. The Panel noted that the data on file concluded that the percentage change in FEV_1 from preinhalation to 60 minutes post-inhalation was statistically significantly higher in the Oxis group compared to the salmeterol group. The p value for the between treatment comparison was $p=0.0001$. Adjacent to the claim at issue was an asterisk referring the reader to the footnote which stated 'Compared with baseline'. The Panel noted its comments in this regard above. The Panel noted that the poster described SRaw as a measure of lung function and considered both FEV_1 and SRaw measurements were relevant. The Panel noted that the improvement in lung function from baseline as measured by FEV_1 was greater in the Oxis group than the improvement from baseline in the salmeterol group. This difference had achieved statistical significance. On balance the Panel considered that the claim was not misleading and was capable of substantiation. No breach of the Code was ruled.

In relation to the claim 'Oxis Turbohaler 12 has a fast onset of action with bronchodilation starting at between 1 to 3 minutes after inhalation', the complainant said that this also was referenced to a poster and data on file. A poster was not an adequate vehicle for proof of effect and such a claim could not be substantiated by 'data on file' only.

The Panel noted that the summary of product characteristics (SPC) stated that 'The bronchodilating effect sets in rapidly within 1-3 minutes after inhalation …'. The claim was consistent with the SPC. The Panel also noted the conclusions of the abstract, Seberova E (1999). The Panel considered that the claim was not misleading and was substantiated by the SPC. No breach of the Code was ruled.

A general practitioner complained about a 'Dear Doctor' letter (ref OXIS 00 6120 D) about Oxis Turbohaler 12 (eformoterol) produced by AstraZeneca UK Limited. The letter was headed 'Give long lasting bronchodilation the green light' and discussed Oxis Turbohaler 12 with regard to duration of bronchodilation and onset of action. The letter was sent in June 2000 to approximately 38,000 GPs.

When writing to the respondent the Authority drew attention to the requirements of Clause 7.3 in addition to those clauses mentioned by the complainant.

1 Claims: 'Oxis Turbohaler 12 may require less use of rescue medication compared with those taking salmeterol…' and 'Oxis Turbohaler 12 has also been shown to deliver significantly greater improvement in lung function 60 minutes after administration with salmeterol 50mcg'.

COMPLAINT

The complainant noted that each claim at issue was referenced to references 2 and 3. The complainant noted that Reference 2 referred to Sill V *et al*, a poster presented at the European Respiratory Society Annual Congress, September 19-23 1998, and data on file OXI/009/DEC 98. Reference 3 was data on file; OXI\012\JUN 99. The complainant alleged that the claims did not comply with Clauses 7.2 and 11.2 of the Code. The complainant did not think that a poster was an adequate vehicle for proof of effect. Such a comparison claim could not be substantiated by 'data on file' only.

RESPONSE

AstraZeneca noted that the two comparative claims at issue were referenced to a poster by Sill (1998) and Data on File (OXI\012\JUN 99), copies of which were provided. The abstract and poster were presented at the European Respiratory Society Annual Congress 1998; the abstract was subsequently published in the European Respiratory Journal 1998; Sill's study was sponsored by Astra Germany and a paper was published in German. This did not contain some of the data presented in the poster, hence the use of the poster and supplementary data on file. The analyses presented in the data on file were additional to those presented in the paper, abstract and poster. Posters and data on file were established and accepted forms of referencing data in the substantiation of claims used in promotional material.

Sill's study was a randomised, multicentre, international study performed according to GCP (Good Clinical Practice). Ninety-nine patients were randomised into the two treatment arms: Oxis Turbohaler 12 twice daily and salmeterol 50mcg twice daily. The two groups were well matched for both demographic and lung function baseline characteristics.

AstraZeneca referred to the claim 'Oxis Turbohaler 12 may require less use of rescue medication compared with those taking salmeterol…'

During the study, patients in both treatment arms maintained diaries recording the use of terbutaline as relief medication. An additional statistical analysis of this parameter studied the reduction in use of the relief medication compared to the run-in period. There was clearly a reduction in the amount of relief medication in both groups. However, the change in mean number of rescue inhalations per day was significantly greater in the Oxis group (p=0.0016). Therefore, on the basis of this analysis, AstraZeneca considered the claim that patients treated with Oxis Turbohaler 12 might use less relief medication than salmeterol to be substantiated and reflect the balance of evidence.

AstraZeneca then considered the claim 'Oxis Turbohaler 12 has also been shown to deliver significantly greater improvement in lung function 60 minutes after administration compared with salmeterol 50mcg'. AstraZeneca noted that the study was specifically designed to measure lung function at fixed time points, including 60 minutes, and statistically powered to detect differences at these time points. The percentage change in FEV_1 from pre-inhalation to 60 minutes post inhalation was significantly higher in the Oxis Turbohaler group compared to the salmeterol group; p value for between treatment comparison: p=0.0001.

AstraZeneca considered that these claims were substantiated and that the poster and data on file together provided adequate proof of effect and denied any breach of Clauses 7.2, 7.3 and 11.2 of the Code.

PANEL RULING

The Panel noted that the claims at issue were referenced to a poster and data on file. Such references were not prohibited *per se* under the Code which required each claim to be capable of substantiation and substantiation to be provided on request. The issue therefore was whether each claim could be substantiated by the data provided.

The Panel considered the first claim, 'a study has shown patients on Oxis Turbohaler 12 may require less use of rescue medication compared with those taking salmeterol breath-activated multi-dose inhalers.' The Panel noted that the Sill *et al* (1998) poster stated that the trial was a randomised open study in 102 patients with moderate asthma designed to compare the onset of action of Oxis Turbohaler and salmeterol. The data on file OXI\012\JUN 99 stated that its analysis was additional to those presented in the published paper, abstract and poster. It analysed the change in terbutaline use from the pre-trial phase to the treatment phase. The mean number of rescue inhalations per day in the pre-treatment and treatment phase was 3.0 ± 2 and 0.8 ± 1.1 for Oxis and 2.1 ± 1.8 and 1.3 ± 1.6 for salmeterol. The change in the mean number of rescue inhalations per day from the pre-treatment to the treatment phase was –2.2 ± 1.8 for Oxis and -0.8 ± 1.1 for salmeterol. The p value was stated to be p=0.0016. The data on file concluded that the reduction in rescue medication from pre-trial to treatment phase was significantly greater in the Oxis Turbohaler group compared to the salmeterol group.

The Panel noted that adjacent to the claim at issue on the 'Dear Doctor' letter was an asterisk which referred the reader to a footnote at the bottom of the page which read 'compared with baseline'. The Panel noted that it was an accepted principle under the Code that a main claim could not be qualified by a footnote. The Panel considered that the claim at issue gave the impression that patients in the Oxis group might have used significantly less rescue medication

than patients in the salmeterol group; the data on file, however, analysed the change in use of rescue medication within each patient group and then compared the change in mean number of rescue inhalations per day with Oxis to that with salmeterol. The Panel noted that the salmeterol group started with a lower level of pre-trial rescue medication usage. The Panel noted that such analysis was not a primary or secondary end point of the study. The Panel noted that the term 'may' was used. On balance, the Panel considered that the claim was not misleading and was capable of substantiation. No breach of Clauses 7.2 and 7.3 were ruled.

The Panel noted that the complainant had alleged a breach of Clause 11.2 of the Code which required, *inter alia,* quotations from medical and scientific literature to accurately reflect the meaning of the author. The relevant supplementary information stated that 'Care should be taken in quoting from any study or the like to ensure that it does not mislead as to its overall significance'. The Panel noted that the claim at issue was not a quotation. Clause 11.2 was not relevant. No breach of Clause 11.2 was ruled.

The Panel then considered the claim 'Oxis 12 Turbohaler has also been shown to deliver significantly greater improvement in lung function 60 minutes after administration compared to salmeterol 50mcg.' The Panel noted that Sill *et al* was designed to measure specific airway resistance at prespecified time points; 2, 5, 10, 20 and 60 minutes after inhalation. Additionally FEV_1 was measured at 10, 20 and 60 minutes after inhalation. The poster stated that two minutes after inhalation of one dose of Oxis a medium reduction of 29% in specific airway resistance (SRaw) was observed. 'In contrast there was no change in the Serevent treated group (SRaw =+1%). This difference was of high statistical significance ($p<0.0001$)'. This data was reflected in the abstract. The Panel noted that Figure 1 of the poster, a graph depicting the reduction in SRaw from baseline of salmeterol and Oxis between 0 and 60 minutes, whilst indicating between group difference did not indicate the statistical significance of this difference as no p values were provided. The between group differences appeared to be markedly less at 60 minutes than at 2 minutes. The Panel did not know whether the difference at 60 minutes was statistically significant. The Panel noted that data on file OXI\012\Jun 99 concluded that the percentage change in FEV_1 from preinhalation to 60 minutes post-inhalation was statistically significantly higher in the Oxis group compared to the salmeterol group. The p value for the between treatment comparison was $p=0.0001$.

The Panel noted that adjacent to the claim at issue was an asterisk referring the reader to the footnote which stated 'Compared with baseline'. The Panel noted its comments in this regard above. The Panel noted that the poster described SRaw as a measure of lung function and considered both FEV_1 and SRaw measurements were relevant.

The Panel noted that the improvement in lung function from baseline as measured by FEV_1 was greater in the Oxis group than the improvement from baseline in the salmeterol group. This difference had achieved statistical significance. On balance the Panel considered that the claim was not misleading and was capable of substantiation. No breach of Clauses 7.2 and 7.3 was ruled. The Panel noted its comments regarding Clause 11.2 above and considered that they applied here. No breach of Clause 11.2 was ruled.

2 Claims: 'Oxis Turbohaler 12 has a fast onset of action with bronchodilation starting at between 1 to 3 minutes after inhalation'.

COMPLAINT

The complainant noted that the claim was referenced to reference 4; Seberova E *et al*, Poster presented at the American Thoracic Society International Conference, April 1999 and data on file OX1\014\MAR\00. Similarly, the complainant alleged that this claim did not comply with Clauses 7.2 and 11.2 of the Code. A 'poster' was not an adequate vehicle for proof of effect. Such a claim could not be substantiated by 'data on file' only.

RESPONSE

AstraZeneca stated that the claim at issue was in accordance with the summary of product characteristics (SPC), which stated that 'The bronchodilating effect [of Oxis] sets in rapidly, within 1-3 minutes after inhalation…' In further support of this claim work by Seberova (1999) was cited. This poster was presented at the American Thoracic Society International Conference, 1999. This multicentre, randomised, double blind, double dummy, crossover trial in 36 patients compared Oxis Turbohaler 6 and 12, and salbutamol 100 and 200mcg in terms of their onset of action. The primary variable of efficacy was the FEV_1 value 3 minutes after dose intake; Oxis Turbohaler had an onset on action of 1-3 minutes.

AstraZeneca considered that these claims were substantiated and that poster data and data on file together provided adequate proof of effect and denied any breach of Clauses 7.2, 7.3 and 11.2.

AstraZeneca noted that The European Respiratory Society Annual Congress and American Thoracic Society were both well respected and prestigious meetings attended by the international medical and scientific community engaged in respiratory medicine. Similarly, The European Respiratory Journal and American Journal Respiratory Critical Care Medicine were held in equally high esteem as a medium for communicating clinical and scientific data within respiratory medicine.

PANEL RULING

The Panel noted that Section 5.1 of the SPC headed 'Pharmacodynamic properties' stated that 'The bronchodilating effect sets in rapidly within 1-3 minutes after inhalation…'. The claim was consistent with the SPC. The Panel also noted that the abstract, Seberova E (1999), concluded that Oxis had as rapid an onset of action as salbutamol when given at recommended doses. The data on file, OXI/014/MAR/00, which presented data taken from a poster of the study by Seberova, stated that Oxis

had an onset of action of 1-3 minutes, as shown when comparing mean FEV_1 change over baseline compared with salbutamol pMDI.

The Panel considered that the claim was not misleading and was substantiated by the SPC data. No breach of Clauses 7.2 and 7.3 was ruled. The Panel noted its comments on Clause 11.2 at point 1 above and ruled no breach of that clause.

Complaint received **5 July 2000**

Case completed **25 September 2000**

CASE AUTH/1049/7/00

DIRECTOR/PARAGRAPH 16 v ASTA MEDICA

Sunglasses offer

During its consideration of Case AUTH/1038/6/00 concerning the promotion of Optilast by Asta Medica, the Panel noted that a mailing to doctors included an offer of a free pair of Optilast sunglasses and queried whether the requirements of the Code had been met in that the sunglasses should be relevant to the profession of the recipient and cost no more than £5 excluding VAT. The Panel decided that the matter should be taken up with Asta Medica in accordance with Paragraph 16 of the Constitution and Procedure for the Authority.

The Panel noted from Asta Medica's response that the cost per pair of sunglasses was £1.78 excluding VAT and that they therefore came within the limit on cost. The Panel did not, however, consider that a pair of sunglasses was relevant to the practice of medicine. A breach of the Code was ruled.

During its consideration of Case AUTH/1038/6/00 concerning the promotion of Optilast by Asta Medica Limited, the Panel noted that a mailing to doctors included an offer of a free pair of Optilast sunglasses.

COMPLAINT

The Panel queried whether the offer of sunglasses met the requirements of Clauses 18.1 and 18.2 of the Code and the relevant supplementary information. A promotional aid could not cost a company more than £5 (excluding VAT) and the item had to be relevant to the recipient's profession. The Panel did not consider that providing a pair of sunglasses was necessarily appropriate. The Panel requested that the matter be taken up with Asta Medica in accordance with Paragraph 16 of the Constitution and Procedure for the Authority.

RESPONSE

Asta Medica stated that one pair of sunglasses cost £1.78. The company submitted that the hayfever season brought specific problems to sufferers and medical practitioners were not immune. It was the intention to offer sunglasses during this period of brighter weather when the incidence of seasonal allergic conjunctivitis was at its peak. A low cost pair of sunglasses would be treated as a disposable item that would be left in the car for convenient use when making house calls in the summer season.

The company submitted that the item might well facilitate the execution of a medical practitioner's duties and was in the company's view a general low cost, utility item relevant to their work.

PANEL RULING

The Panel noted that a copy invoice provided by Asta Medica confirmed that the cost per pair of sunglasses was £1.78 excluding VAT; they therefore came within the limit of £5 excluding VAT which applied to promotional aids. The Panel did not, however, consider that a gift of a pair of sunglasses was relevant to the practice of medicine; they would not make a practical contribution to the way in which a doctor performed his professional role. The sunglasses did not meet the provisions of Clause 18.2 and a breach of Clause 18.1 of the Code was ruled.

Proceedings commenced **26 June 2000**

Case completed **17 July 2000**

CONSULTANT PHYSICIAN v AVENTIS PHARMA

Amaryl leaflet

A consultant physician complained about a leaflet for Amaryl (glimepiride) which was left by Aventis Pharma representatives after interviews with doctors. The second page was headed 'Weight neutral metabolic control'. It referred to weight stability and included a graph headed 'Mean change in body weight by BMI [body mass index] classes'. The graph showed mean weight change in kg for patients with BMI of <19kg/m^2, 19-25kg/m^2, 26-30kg/m^2. and >30kg/m^2. The claims 'Overall patients lost a mean of 1.4kg' and 'The greatest weight loss was seen in obese patients (BMI >30kg/m^2)' appeared beneath the graph. The complainant stated that he had recently been given a most convincing argument by an Aventis representative regarding the beneficial effect on weight reduction of glimiperide in the more overweight members of the diabetic population. The complainant queried whether the data (to be published in due course) were valid and whether the message was misleading. The absolute weight reduction was quoted rather than the proportionate weight reduction. The complainant stated that his detailed knowledge of statistics was now becoming a little rusty but was it not inevitable that in a population trying to lose weight the absolute weight loss would always be greatest in those who were further from the mean ('regression towards the mean')?

It would help the complainant greatly to know whether these data were in fact valid, as this could have a significant effect on prescribing, or whether the data should have been more accurately portrayed as proportionate weight loss.

The Panel noted Aventis' submission that weight control was an important issue in diabetes. It also noted that the data shown in the graph were from a PMS study after eight weeks of treatment and that the study was a large study (n=19,097). These details were given in the heading to the graph or immediately beneath the heading. The Panel did not accept that it was unreasonable to use absolute weight reduction. Aventis had stated that it was the usual way weight was discussed by both patients and doctors and also the way that such data were reported in journals such as The Lancet. The third page of the leaflet showed a decrease in mean weight change at 4, 12 and 18 months. The Panel noted Aventis' submission regarding the alternative methods of presenting the data. Either absolute or percentage changes could be calculated and the data used could be either all patients with pre- and post-treatment weights or all patients who completed the eight weeks PMS protocol. The various presentations of the data had been supplied. The Panel noted the submission that Aventis had not necessarily used the most flattering method of presentation.

The Panel noted the various presentations of the data. It noted that little information had been supplied about the design of the study. Nevertheless, it did not accept that the data were misleading as alleged. No breach of the Code was ruled.

A consultant physician complained about the promotion of Amaryl (glimepiride) by Aventis Pharma Ltd. The material at issue was a leaflet (ref AML218) which was distributed by the representative once an interview had been granted by the doctor.

Page 2 of the leaflet was headed 'Weight neutral metabolic control'. It referred to weight stability and included a graph headed 'Mean change in body weight by BMI [body mass index] classes'.

The graph showed mean weight change in kg for patients with BMI of <19kg/m^2, 19-25kg/m^2, 26-30kg/m^2. and >30kg/m^2. The claims 'Overall patients lost a mean of 1.4kg' and 'The greatest weight loss was seen in obese patients (BMI >30kg/m^2)' appeared beneath the graph. The data was from a post-marketing surveillance study conducted over a period of eight weeks.

COMPLAINT

The complainant stated that he had recently been given a most convincing argument by an Aventis representative regarding the beneficial effect on weight reduction of glimiperide in the more overweight members of the diabetic population. The complainant had been told that the data was to be published in due course.

The complainant queried whether the data were valid and whether the message was misleading.

The absolute weight reduction was quoted rather than the proportionate weight reduction. The complainant stated that his detailed knowledge of statistics was now becoming a little rusty but was it not inevitable that in a population trying to lose weight the absolute weight loss would always be greatest in those who were further from the mean ('regression towards the mean')?

The complainant stated that it would help him greatly to know whether these data were in fact valid, as this could have a significant effect on prescribing, or whether the data should have been more accurately portrayed as proportionate weight loss.

RESPONSE

Aventis Pharma stated that the issue of weight was a pertinent one and it believed that the data presented were valid and not misleading. An important question was why weight should be an issue worth mentioning in a piece about a sulphonylurea.

It was well-known that obesity was an important issue in diabetes. Being overweight was the only major modifiable risk factor for developing type 2 diabetes and it was also an important obstacle to the treatment of established type 2 diabetes. It had been estimated that over 90% of patients with type 2 diabetes were overweight and a gradual increase in weight was an almost universal finding over time in patients with type 2 diabetes. Reducing obesity in patients with type 2 diabetes was therefore of crucial importance.

For many years sulphonylureas had been regarded as first line treatment for type 2 diabetes, however, there had been concerns about their impact on weight. These doubts were related to their mode of action (increasing insulin output by the pancreas) which might lead to increases in weight on theoretical grounds. These concerns were supported by some early data on chlorpropramide and had been fuelled by the supporters of the use of metformin which had been shown to have less impact on weight than glibenclamide or insulin. However, the data on glibenclamide were not necessarily applicable to other sulphonylureas: for example there was data to show that gliclazide had no adverse effect on weight and the chapter on sulphonylureas in the International Textbook of Diabetes Mellitus set little store by the suggestion that sulphonylureas caused significant weight gain stating that there was little scientific data to support the proposal. Published data from a comparative study of glibeclamide versus glimepiride indicated that neither medicine had a particularly marked effect on weight in the setting of a randomised controlled trial (Draeger 1996). However, three post marketing surveillance (PMS) studies of glimepiride had all shown small but consistent reductions in weight in patients who had received glimepiride in routine clinical practice (Aventis data on file). Given that weight gain was the expected outcome in type 2 diabetics this data was of considerable clinical interest.

Aventis stated that the data on which the graph on page 2 of the item was based were drawn from the final report and tables for the German PMS study (Study HOE 490/3/D/C001/96), a study which recruited over 22,000 patients. From a statistical point of view, studies of this size produced data which were very robust. Therefore, there could be no doubt about the validity of the data.

Aventis' view was that the data were not misleading but had been misunderstood.

It was suggested by the complainant that quoting absolute weight reduction was inappropriate. In fact this was not only the usual way weight reduction was discussed by both patients and doctors, but also it was the way such data were reported in journals such as The Lancet.

The complainant also asked would absolute weight loss not be greatest in those furthest from the mean? The answer to this was no (in terms of the expected outcome), for two reasons: firstly, those who were most obese were the ones who found it most difficult to lose weight and secondly, there were two populations furthest from the mean – those most above it and those most below it. Those most above it were the ones who had most difficulty with their weight and weight loss was likely to be small as a result. Weight loss in those underweight was not likely to be large since they were underweight already.

The complainant also raised the issue of regression to the mean. This term was coined to describe observations about the characteristics of offspring by comparison to their parents (Bland 1987). It was not a relevant concept in the context of changes in the weight of patients with type 2 diabetes on treatment with sulphonylureas.

The final possibility was that the presentation of the data in absolute terms rather than percentage terms in the graph was misleading. To allow this matter to be judged by the Panel, Aventis included two sets of tables and graphs which showed the two ways the data could be presented. Either absolute or percentage changes could be calculated and the data set used could be either all patients with pre- and post-treatment weights or all patients who completed the eight week PMS protocol (the latter was the version used in the item complained about). There was no indication that any presentation of the data told a different or more favourable story. Indeed the presentation used might not be the most flattering of those available.

In summary the issue of weight was a pertinent one and Aventis believed that the data presented were valid and not misleading.

PANEL RULING

The Panel noted the submission that weight control was an important issue in diabetes. It also noted that the data shown in the graph were from a PMS study after eight weeks of treatment and that the study was a large study (n=19,097). These details were given in the heading to the graph or immediately beneath the heading. The Panel noted that it had been provided with very little detail about the study arrangements. It was not necessarily unacceptable to refer to unpublished PMS study data in promotional material.

The Panel did not accept that it was unreasonable to use absolute weight reduction. Aventis stated that it was the usual way weight was discussed by both patients and doctors and also the way that such data were reported in journals such as The Lancet. Page 3 of the leaflet showed a decrease in mean weight change at 4, 12 and 18 months.

The Panel noted Aventis' submission regarding the alternative methods of presenting the data. Either absolute or percentage changes could be calculated and the data used could be either all patients with pre- and post-treatment weights or all patients who completed the eight weeks PMS protocol. The various presentations of the data had been supplied. The Panel noted the submission that Aventis had not necessarily used the most flattering method of presentation.

The Panel noted the various presentations of the data. It noted that little information had been supplied about the design of the study. Nevertheless, it did not accept that the data presented on page 2 of the leaflet were misleading as alleged. No breach of Clause 7.2 of the Code was ruled.

Complaint received **10 July 2000**

Case completed **24 August 2000**

HOSPITAL DRUG INFORMATION PHARMACIST v SANOFI-SYNTHÉLABO and BRISTOL-MYERS SQUIBB

Plavix promotional card

A hospital drug information pharmacist complained about a promotional card for Plavix (clopidogrel) produced jointly by Sanofi-Synthélabo and Bristol-Myers Squibb and issued as a supplement to Hospital Update. One side of the card was headed 'Management Summary' and 'Prescribing antiplatelet therapy in atherosclerotic disease: where to consider clopidogrel?', beneath which a flow chart set out various antiplatelet therapy options in patients with 'clinically manifest atherosclerosis'. The complainant said that the flow diagram mentioned transient ischaemic attack (TIA) and the clear implication was that Plavix could be used in TIA, when in fact this was not a licensed indication. Also, there was no indication on the chart that there should be a delay when instituting therapy with clopidogrel (ie 7 days for ischaemic stroke, a few days for myocardial infarction (MI). The pharmacy department had seen several instances recently of doctors prescribing clopidogrel for TIAs, and also immediately after ischaemic events and MI. The complainant had not been able to establish whether the doctors were directly influenced by these cards but it did seem to be too much of a coincidence.

The Panel noted that the patient group to which the card related was described as those with 'Clinically manifest atherosclerosis (MI, TIA/ischaemic attack or ischaemic stroke, or PVD [peripheral vascular disease])'. Another section of the flow chart referring to patients who were aspirin intolerant stated '1. Consider clopidogrel. 2. Consider dipyridamole, if stroke/TIA and cardiovascular risk is low.' The summary of product characteristics (SPC) for Plavix described those patients in whom Plavix was licensed to reduce atherosclerotic events; namely patients with a history of symptomatic atherosclerotic disease defined by ischaemic stroke (from seven days until less than six months) myocardial infarction (from a few days until less than 35 days) or established peripheral arterial disease.

The Panel noted that the description of the patient group with clinically manifest atherosclerosis on the card was different to that in the SPC in that it included patients with TIA/ischaemic attack. The Panel considered that the card was misleading about the patient population for which Plavix was indicated. The Panel ruled a breach of the Code. The Panel considered that the second reference to TIA on the flow chart was different. The reference was in relation to aspirin intolerant patients with the recommendation '1. Consider clopidogrel. 2. Consider dipyridamole, if stroke/TIA and cardiovascular risk is low'. It was not clear whether the warning 'if stroke/TIA and cardiovascular risk is low' applied to dipyridamole alone or to both clopidogrel and dipyridamole. Nevertheless the Panel did not consider that this section of the flow chart referred to Plavix treating or reducing the risk of TIA nor did it state or imply that Plavix was indicated to treat patients with a history of TIA. Rather one interpretation was that [in patients with clinically manifest atherosclerosis] treatment with clopidogrel or dipyridamole should be considered in aspirin intolerant patients if stroke/TIA and cardiovascular risk was low. The Panel did not consider that the second reference to TIA was in itself misleading about the licensed indication of Plavix. No breach of the Code was ruled in that regard.

In relation to the allegation that the promotional item ought to mention the delay prior to starting therapy with Plavix, the Panel noted that Plavix was limited to patients with ischaemic stroke from seven days until less than six months and patients with myocardial infarction from a few days until less than 35 days. The Panel noted the submission that the item was a flow chart for the management of disease and of where Plavix might fit in that management process. Detailed clinical information was not provided for any product mentioned on the item; it showed the reader when to consider Plavix. On balance the Panel did not consider the item misleading as alleged and no breach of the Code was ruled.

A hospital drug information pharmacist complained about a promotional card (ref PLA-00/018) for Plavix (clopidogrel) produced jointly by Sanofi-Synthélabo and Bristol-Myers Squibb Pharmaceuticals Limited and issued as a supplement to Hospital Update December 1999. One side of the card was headed 'Management Summary' and 'Prescribing antiplatelet therapy in atherosclerotic disease: where to consider clopidogrel?', beneath which a flow chart set out various antiplatelet therapy options in patients with 'clinically manifest atherosclerosis'.

COMPLAINT

The complainant stated that the left-hand side of the flow diagram mentioned transient ischaemic attack (TIA) and again near the bottom left. The clear implication on following the arrows was that Plavix could be used in TIA, when in fact this was not a licensed indication.

Also, there was no indication on the chart that there should be a delay when instituting therapy with clopidogrel (ie 7 days for ischaemic stroke, a few days for myocardial infarction (MI)).

The complainant had raised both these points with one of the companies and had spoken to its information department on 14 and 16 June whereupon he was assured he would be contacted by either the medical director or marketing manager the following Monday or Tuesday. No call was received

so the complainant rang the information department again on 28 June. He was unable to speak directly to his previous contact as a meeting was taking place, but was told he would be called back as soon as possible. He received no call and no one had been in contact with him since then. The pharmacy department had seen several instances recently of doctors prescribing clopidogrel for TIAs, and also immediately after ischaemic events and MI. The complainant had not been able to establish whether the doctors were directly influenced by these cards but it did seem to be too much of a coincidence.

RESPONSE

Sanofi-Synthélabo and Bristol-Myers Squibb submitted a joint response to the complainant.

The companies stated that the summary of product characteristics (SPC) for Plavix showed that its licensed indication was for the reduction of atherosclerotic events (myocardial infarction, stroke, death due to vascular causes) in patients with a history of symptomatic atherosclerotic disease defined by ischaemic stroke (from seven days until less than six months), myocardial infarction (MI) (from a few days until less than 35 days) or established peripheral vascular disease. The licence was granted on the basis of the CAPRIE trial involving more than 19,000 patients and published in The Lancet in 1996 and this trial was detailed in the SPC. It was important to note that the inclusion criteria for this large multicentre, multinational study were: history of myocardial infarction, ischaemic stroke or peripheral vascular disease; patients with prior atherothrombotic events or atherosclerotic disease in more than one arterial bed. These criteria resulted overall in the recruitment of a substantial number of patients with atherosclerosis, including some 10% with a history of TIA, being randomised into each treatment group. In fact 19% of patients with a history of stroke had suffered prior TIA. As the licensed indications for clopidogrel were specifically based on these inclusion criteria, it was pertinent to take them into account when considering the complaint that TIA was wrongly incorporated into the chart in question.

TIA was mentioned twice on the flow chart:

Firstly, on the left-hand side, the starting point for the chart. The chart related to antiplatelet therapy in the management of clinically manifest atherosclerotic disease of a variety of forms, including TIA.

Secondly, TIA was mentioned below the 'aspirin intolerant' box. In this case, the emphasis was on the possible management choices for a very small sub-group of patients for whom the therapeutic options were extremely limited.

The companies submitted that TIA was a very important precursor symptom to ischaemic stroke as a result of carotid occlusion. In fact, up to 75% of patients suffering from carotid stroke would have had a known prior TIA. Guidelines from the ACCP Consensus Conference on Antithrombotic Therapy stated quite clearly that every patient who had experienced an atherothrombotic stroke or TIA and had no contraindications should receive an antiplatelet agent regularly to reduce the risk of recurrent stroke and other vascular events (Albers *et al* 1998).

Furthermore, the British Medical Journal (BMJ) collaborative overview of randomised trials of antiplatelet therapy was equally clear in its recommendation. Their review concluded that, among more than 10,000 patients with a prior history of stroke or TIA, antiplatelet therapy produced a highly significant reduction in the risk of suffering another vascular event (Antiplatelet – Trialists Collaboration).

The companies stated that TIA was a symptom of atherosclerotic disease, and a precursor to ischaemic stroke in many patients. Whilst it was not detailed in the list of symptoms in the SPC, it was a part of the same disease process. The companies pointed to Case AUTH/819/1/99 as a precedent for this case. Whilst, in that case, Zocor was not indicated specifically for reducing the risk of angina, it was accepted that angina was one of the clinical manifestations of the underlying disease process for which Zocor was indicated. This was equally true for Plavix in this case.

The complainant was correct in noting that the flow chart did not mention the delay prior to starting therapy with Plavix. It was important to recognise that this was a flow chart for the management of disease and of where clopidogrel might fit in that management process. It was not a piece detailing the SPC of any product. Indeed other products were mentioned, with no reference to important contraindications or special precautions relating to their usage. The appropriate prescribing of Plavix and other products was detailed in their respective SPCs, and was related to individual patient profiles. The companies could not comment on the complainant's assertion that doctors in his hospital chose to use Plavix immediately following ischaemic events. This was based on their assessment of the needs of the patient before them.

In answer to the final allegation regarding the Medical Information Department, the records indicated that the complainant contacted the Medical Information Department at Sanofi-Synthélabo regarding this chart on 14 June, and that the department returned his call on 16 June to provide the required information. During this discussion, as the complainant indicated that he wished to pursue some of these points further, it was agreed another member of staff would contact him by telephone on 19 June. Although the complainant was telephoned on that day as arranged, he was not available and so a message was left for him to call back. A subsequent telephone call from him to the Medical Information Department on 28 June was apparently not adequately responded to.

The companies apologised to the complainant if he felt that the response was inadequate in this case and would address their standard operating procedure to ensure that this situation did not recur.

Bristol-Myers Squibb and Sanofi-Synthélabo stated that based on the above, the general nature of the flow chart, and the continuum which existed between TIA and ischaemic stroke, as part of the same atherosclerotic disease process, the companies did not accept that this chart promoted the use of clopidogrel outside the terms of its product licence.

The flow chart in question was prepared recently at the companies' request by an independent specialist, and was based on information and practice, which were, and continued to be, current. It included lifestyle and other management options in addition to drug therapy, and referred to antiplatelet agents other than clopidogrel as options in the management of atherosclerotic disease. It was not therefore in breach of Clause 7.2.

PANEL RULING

The Panel examined the item in question and noted that the patient group to which it related was described as those with 'Clinically manifest atherosclerosis (MI, TIA/ischaemic attack or ischaemic stroke, or PVD [peripheral vascular disease])'. Another section of the flow chart referring to patients who were aspirin intolerant stated '1. Consider clopidogrel. 2. Consider dipyridamole, if stroke/TIA and cardiovascular risk is low.'

The Panel noted the licensed indication for Plavix as stated in the SPC and referred to by Bristol-Myers Squibb and Sanofi-Synthélabo above. The Panel also noted that data from the CAPRIE study was provided at Section 5.1 of the SPC, headed 'Pharmacodynamic properties'. The history of TIA in the patient population examined in the CAPRIE study was not stated in the SPC.

The Panel queried whether the companies' submission regarding the percentage of patients with a history of TIA in each patient subgroup in the CAPRIE study was correct. The CAPRIE study, Table 4, stated that 19% of patients in each arm of the stroke subgroup had a history of TIA/RIND [reversible ischaemic neurological deficit]; the data did not relate to TIA alone. In the MI subgroup the figures were 3% in the clopidogrel arm and 2% in the aspirin arm. The population studied comprised subgroups of patients with atherosclerotic vascular disease manifested as recent ischaemic stroke, recent myocardial infarction or symptomatic peripheral arterial disease. The Panel noted that whilst some patients in each subgroup in the CAPRIE study had a history of TIA, such patients did not comprise a specific subgroup.

The Panel noted that Case AUTH/819/1/99 concerned the promotion of Zocor by Merck Sharp & Dohme. Bristol-Myers Squibb was concerned about two claims that Zocor significantly reduced the incidence of angina, by 26% ($p<0.0001$), and that Zocor reduced the risk of new or worsening angina by 26% in post-MI and angina patients. Zocor was indicated for patients with coronary heart disease with a plasma cholesterol level of 5.5mmol/l or greater to reduce the risk of mortality, reduce the risk of coronary death and non-fatal myocardial infarction, reduce the risk for undergoing myocardial revascularisation procedures, and to slow the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions. Bristol-Myers Squibb alleged that the claim that Zocor reduced the risk of new or worsening angina was outside the licensed indications and in breach of the Code. The Panel considered that angina was one of the clinical manifestations of the underlying disease process for which Zocor was indicated. The Panel did not consider that the claims promoted Zocor outside the terms of its licence. No breach of the Code was ruled. Upon appeal, the Appeal Board considered that general practitioners would be familiar with statins and their uses and know that they were indicated to lower raised cholesterol levels and not to treat angina *per se*, ie they were licensed to treat the underlying pathology and not the presenting symptom. The Appeal Board noted that the claim in the advertisement referred to reducing the risk of new or worsening angina in post-MI and angina patients. The claim did not refer to treating angina. This was an important difference as the term risk implied prevention or attenuation of the rate of progression of new or worsening angina. The Appeal Board upheld the Panel's ruling of no breach.

Turning to the present case the Panel noted that the therapeutic indication section of the SPC described those patients in whom Plavix was licensed to reduce atherosclerotic events; namely patients with a history of symptomatic atherosclerotic disease defined by ischaemic stroke (from 7 days until less than six months) myocardial infarction (from a few days until less than 35 days) or established peripheral arterial disease. The Panel noted that the description of the patient group with clinically manifest atherosclerosis on the Plavix promotional card was different to that in the SPC in that it included patients with TIA/ischaemic attack.

The Panel considered that the card was misleading about the patient population for whom Plavix was indicated. The Panel ruled a breach of Clause 7.2.

The Panel considered that the second reference to TIA on the flow chart was different. The reference was in relation to aspirin intolerant patients with the recommendation '1. Consider clopidogrel 2. Consider dipyridamole, if stroke/TIA and cardiovascular risk is low'. The Panel considered that it was not clear whether the warning 'if stroke/TIA and cardiovascular risk is low' applied to dipyridamole alone or to both clopidogrel and dipyridamole. Nevertheless the Panel did not consider that this section of the flow chart referred to Plavix treating or reducing the risk of TIA nor did it state or imply that Plavix was indicated to treat patients with a history of TIA. Rather one interpretation was that [in patients with clinically manifest atherosclerosis] treatment with clopidogrel or dipyridamole should be considered in aspirin intolerant patients if stroke/TIA and cardiovascular risk was low.

The Panel noted its comments on the patient population identified on the promotional card above, however the Panel did not consider that the second reference to TIA was in itself misleading about the licensed indication of Plavix. No breach of Clause 7.2 was ruled.

The Panel then considered the allegation that the promotional item ought to mention the delay prior to starting therapy with Plavix. The Panel noted that Plavix was limited to patients with ischaemic stroke from 7 days until less than 6 months and patients with myocardial infarction from a few days until less

than 35 days. The Panel noted the submission that the item was a flow chart for the management of disease and of where Plavix might fit in that management process. The Panel noted that detailed clinical information was not provided for any product mentioned on the item; it showed the reader when to consider Plavix. On balance the Panel did not consider the item misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that the complainant had described his contact with the medical information department. The Panel noted the submission that messages had been left for the complainant. It was unfortunate that contact had not been made. The Panel did not consider that the complainant had alleged a breach of the Code in this regard and thus made no ruling on this point.

Complaint received **19 July 2000**

Case completed **4 October 2000**

CASES AUTH/1055/7/00 & AUTH/1056/7/00 *NO BREACH OF THE CODE*

MERCK SHARP & DOHME v PROCTER & GAMBLE and AVENTIS PHARMA

Actonel journal advertisement

Merck Sharp & Dohme complained about promotional materials for Actonel (risedronate) issued by Procter & Gamble and Aventis Pharma, referring in particular to a journal advertisement. The advertisement showed the upper pelvic bone and spine sloping upwards at an angle with the lower part apparently of flawless metal and the upper part of osteoporotic bone. Running up the spine, and located at the junction between the metal and bone portions, was a representation of Mercury, the Roman messenger of the Gods. The advertisement was headed 'New Actonel Proven to significantly reduce vertebral fractures – in just 1 year' beneath which text discussed the need for rapid protection from vertebral fracture in postmenopausal women with established osteoporosis and the vertebral fracture risk reduction in such patients over one and three years.

Merck Sharp & Dohme alleged that the image of a metal spine was misleading as it exaggerated the efficacy of risedronate in the treatment of osteoporosis. The speed of risedronate's action was portrayed by a figure running along a spine, and the magnitude of its efficacy was conveyed by the change from an osteoporotic spine to a metal spine. In comparison to bone, metal would generally be considered much stronger with little liability to fracture. Deformities related to osteoporotic fractures could not be reversed with any kind of treatment. The magnitude of the change portrayed in the image was clearly in excess of what could be expected clinically with risedronate treatment.

The Panel considered that the image conveyed an impression of speed of action and efficacy. This impression was underlined by the heading and the strapline 'Protection that's fast – and lasts.' The Panel noted that whilst the illustration was an artist's representation of these qualities it nonetheless had to comply with the Code. The Panel considered that the magnitude of effect depicted by the change from osteoporotic bone to healthy, perfect bone was not a fair reflection of the data. It exaggerated the response to Actonel and was misleading. Breaches of the Code were ruled.

Upon appeal by Procter & Gamble and Aventis Pharma, the Appeal Board considered that the visual was a striking image designed to catch the reader's eye. It was not meant to be an anatomical representation of the effect of Actonel on the spine. The effect of Actonel on the spine was discussed in the text immediately adjacent to the illustration. The Appeal Board considered that healthcare professionals would be well aware of the effects of osteoporosis and that treatment delayed progression of the disease. The Appeal Board did not consider that the advertisement was misleading or exaggerated as alleged. No breach of the Code was ruled.

Merck Sharp & Dohme Limited complained about promotional materials for Actonel (risedronate sodium) issued by Procter & Gamble Pharmaceuticals, UK Ltd and Aventis Pharma Ltd, referring in particular to a journal advertisement (ref A1346). The advertisement showed the upper pelvic bone and spine sloping upwards at an angle with the lower part apparently of flawless metal and the upper part of osteoporotic bone. Running up the spine, and located at the junction between the metal and bone portions of it, was a male figure wearing a winged helmet, a loin cloth and winged sandals.

The advertisement was headed 'New Actonel Proven to significantly reduce vertebral fractures – in just 1 year' beneath which text discussed the need for rapid protection from vertebral fracture in postmenopausal women with established osteoporosis and the vertebral fracture risk reduction in such patients over one and three years.

COMPLAINT

Merck Sharp & Dohme stated that it believed that the image used in risedronate promotional materials of a metal spine was misleading as it exaggerated the efficacy of risedronate in the treatment of osteoporosis and was therefore in breach of Clauses 7.6 and 7.8 of the Code. Merck Sharp & Dohme had made extensive

efforts to come to an agreement with Procter & Gamble and Aventis regarding this artwork but had been unable to do so. The correspondence was provided.

Merck Sharp & Dohme noted that the speed of risedronate's action was portrayed by a figure representing Hermes running along a spine, and the magnitude of its efficacy was conveyed by the change from an osteoporotic spine to a metal spine. The thoracocervical spine on the right of the picture was clearly markedly osteoporotic with multiple fractures. However, the metal continuation of the spine was completely flawless. In comparison to bone, metal would generally be considered much stronger with little liability to fracture. Deformities related to osteoporotic fractures could not be reversed with any kind of treatment. Two trials of three years' duration with risedronate in patients with osteoporosis had demonstrated increases in bone mineral density of 5.4-5.9% at the lumbar spine and relative risk reductions for new vertebral fractures of 41-44%. The magnitude of the change portrayed in the image was clearly in excess of what could be expected clinically with risedronate treatment, and went beyond what Merck Sharp & Dohme would consider to be illustrative in nature. The supplementary information to Clause 7.6 stated that 'anatomical drawings used to show results from a study must not exaggerate those results.' Merck Sharp & Dohme believed that the image portrayed would be covered by this clause and it also constituted an exaggerated claim in breach of Clause 7.8. This interpretation would seem to be consistent with the judgement in Case AUTH/703/5/98 – illustration of mode of action.

RESPONSE

In a joint response, Procter & Gamble and Aventis Pharma stated that they refuted the allegation that the image of a metal spine was misleading as it exaggerated the efficacy of Actonel in the treatment of osteoporosis. The allegation was based on a misinterpretation of the image question. The image did not portray a measurable effect of Actonel. It conveyed the concept of the need to manage osteoporosis promptly.

The figure depicted was Mercury, known from Roman mythology as the messenger of the gods. Mercury was classically depicted with a winged hat and winged sandals, signifying speed of travel. In this visual, Mercury was sprinting over an image of a vertebral column. The imagery therefore depicted both a messenger and the concept of speed, in the context of osteoporosis as a disease. There were recent data showing one in five postmenopausal women with established osteoporosis fracture again within one year of sustaining an incident vertebral fracture (Lindsay abstract) and the subsequent risk increased with each prevalent fracture (Cooper abstract). These findings were changing the perception of osteoporosis; once seen as a slowly developing condition, it was now known that the rapid progression of the disease from the initial vertebral fracture had significant clinical importance. Mercury was the messenger who was delivering this new message of the need for rapid treatment of postmenopausal osteoporosis to prevent subsequent fractures.

Procter & Gamble and Aventis believed that the use of Mercury to depict the need for rapid management of postmenopausal osteoporosis was not misleading, and therefore that there was no breach of either Clause 7.6 or Clause 7.8.

Procter & Gamble and Aventis did not believe that Case AUTH/703/5/98 was relevant to the visual imagery in question. Case AUTH/703/5/98 referred to artwork representing airway inflammation. However, it referred to specific and measurable representations ('The diameter of the open airway was 2.8cm and in the inflamed airway it was 0.6cm, representing nearly 80% occlusion'), ie a measurable treatment effect. As detailed earlier, the visual imagery used in the Actonel advertisement did not attempt to show any measurable study results. The companies therefore believed that this case bore no relevance to the Actonel advertisement.

Of interest, however, Case AUTH/593/8/97 could be judged as more relevant. This concerned imagery used in promotional materials for a treatment for Alzheimer's disease. The ruling highlighted the point that imagery need not be interpreted literally, and that a degree of artistic licence was acceptable. In particular, the ruling stated that the materials were 'not claiming that the product was the cure' as was the case in the promotional materials for Actonel. Further, the Panel ruled that the Alzheimer's imagery did not convey any 'specific type of improvement or degree of effect', as was again the case in the Actonel imagery.

In conclusion, Procter & Gamble and Aventis believed that their visual portrayed the need to manage osteoporosis promptly in order to prevent further clinical consequences. This was explained fully in the accompanying text which was in itself fully aligned with the approved summary of product characteristics (SPC) for Actonel. The companies therefore believed that the imagery as presented was not misleading or exaggerated as suggested by Merck Sharp & Dohme, and therefore there was no breach of either Clause 7.6 or Clause 7.8.

Merck Sharp & Dohme had stated in its letter that it had made 'extensive efforts to come to an agreement with Procter & Gamble and Aventis regarding this artwork.' Procter & Gamble and Aventis initiated a meeting with Merck Sharp & Dohme on 28 June and explained that they hoped a continuing dialogue could resolve its concerns. Therefore, the companies were surprised to see that Merck Sharp & Dohme had submitted this complaint. Procter & Gamble and Aventis hoped that they had satisfactorily addressed the points raised.

PANEL RULING

The Panel noted that the complaint made by Merck Sharp & Dohme related solely to the imagery involved in relation to efficacy. There was no complaint about speed of action and it did not extend to other matters raised in the correspondence between the parties which had been provided.

The Panel noted that the Actonel SPC stated that it was indicated for the treatment of postmenopausal established osteoporosis to reduce the risk of vertebral fractures. Prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis. To maintain or increase bone mass in postmenopausal women undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses ≥7.5mg/day prednisone or equivalent. Section 5.1 headed 'Pharmacodynamic properties' stated that in preclinical studies risedronate dose dependently increased bone mass and biomechanical skeletal strength. The section subtitled 'Treatment and Prevention of Postmenopausal Osteoporosis' stated that 'In the Multinational and North American studies the incidence of new vertebral fractures was 29.0% and 16.3% in control patients (treated with calcium and vitamin D) and 18.1% and 11.3% in risedronate treated patients respectively'. The treatment of 1000 patients, on average, prevented 100 and 50 new vertebral fractures (NNT 10 and 20) respectively. The effect of treatment was seen as early as the end of the first year. Actonel 5mg daily given for 3 years increased bone mineral density (BMD) relative to control at, *inter alia*, the lumber spine. With regard to corticosteroid induced osteoporosis the SPC stated that Actonel given daily for one year maintained or increased bone mineral density (BMD) relative to control at, *inter alia*, the lumber spine. Actonel 5mg given daily reduced the incidence of vertebral fractures, monitored for safety, relative to control at one year in pooled studies.

The Panel noted the studies referred to by the complainant. Harris *et al* (1999) was a randomized double blind placebo controlled trial of postmenopausal women designed to test the efficacy and safety of Actonel to reduce the risk of vertebral and other fractures in postmenopausal women with established osteoporosis. Over 3 years there was a statistically significant reduction of 41% in the risk of new vertebral fractures compared with placebo ($p=0.003$). A statistically significant reduction of 65% ($p<0.001$) in vertebral fracture risk was seen in the first year of treatment. Over 3 years there was an increase in BMD from baseline at the lumber spine of 5.4%. The study authors concluded that 'The onset of the fracture effect was rapid'. The Panel noted that Reginster *et al* (2000), a 3 year randomized double blind placebo controlled study determined that in postmenopausal women with two or more prevalent vertebral fractures at baseline Actonel 5mg reduced the incidence of vertebral fractures by 61% over 12 months and by 49% over 3 years. The study authors noted that the Actonel patients entering the third year of the study had significantly more prevalent vertebral fractures than the placebo patients entering the third year which may have attenuated the treatment effect toward the end of the study. There were significant differences in spine and hip BMD between Actonel 5mg and placebo after 6 months $p<0.05$. The Panel also noted the comments of Aventis regarding the abstracts, Lindsay (2000) and Cooper (2000).

The Panel noted the supplementary information to Clause 7.6 headed 'Artwork, Illustrations, Graphs and Tables' which stated that 'Care must be taken to ensure that artwork does not mislead as to the nature of a medicine or any claim or comparison…. For example anatomical drawings used to show results from a study must not exaggerate those results'.

The Panel noted that Case AUTH/703/5/98 referred to by Merck Sharp & Dohme concerned a detail aid produced by Merck Sharp & Dohme which depicted an artist's impression of airways inflamed in asthma before and after treatment with Singulair. Glaxo Wellcome alleged that whilst the depiction might be consistent with severe inflammation it could not be substantiated by the data provided and was misleading. The Panel considered that readers would appreciate that the illustrations were schematic. The illustration showed a sequence of events and was not meant to demonstrate an absolute change in size of airways. No breach of the Code was ruled. On appeal the Appeal Board considered that the illustration was misleading as it exaggerated the response to Singulair. A breach of the Code was ruled.

The Panel noted that Cases AUTH/593/8/97 and AUTH/594/8/97 referred to by Aventis concerned an advertisement for Aricept placed by Eisai and Pfizer. The complainant alleged that a photograph of a woman and her mother implied that the mother had improved sufficiently to restore her memory but research trials had failed to establish this sort of improvement. The Panel noted there was data to support an improvement of cognitive function with Aricept and in the face of such improvement the Panel considered that mother and daughter would have cause to look happy. The Panel did not consider the advertisement misleading with regard to the efficacy of Aricept, it was not being claimed that the product was a cure for Alzheimer's disease.

Turning to the present case the Panel considered that the image conveyed an impression of speed of action and efficacy. This impression was underlined by the heading 'New Actonel Proven to significantly reduce vertebral fractures – in just 1 year' and the strapline 'Protection that's fast – and lasts.' The Panel noted that whilst the illustration was an artist's representation of these qualities it nonetheless had to comply with the Code. Whilst the Panel noted the efficacy data in the SPC and its comments on the studies above, it considered that the magnitude of effect depicted by the change from osteoporotic bone to healthy, perfect bone was not a fair reflection of the data. It exaggerated the response to Actonel and was misleading as alleged. Breaches of Clauses 7.6 and 7.8 were ruled.

APPEAL BY PROCTER & GAMBLE AND AVENTIS

The respondent companies stated that the Panel had ruled that the 'magnitude of effect' of Actonel depicted by the 'change from osteoporotic bone to healthy, perfect bone' was not a fair reflection of the data. The Panel had noted the indications for Actonel and the data that supported the claim for reduction in the risk of vertebral fracture within one year. However, the companies did not believe that the visual in question depicted measurable study results. Nor did they believe that the bone depicted was healthy, perfect bone. It was bone covered with mercury, to indicate that Actonel (visualised by

Mercury) touched the bone and had an influence on it. Informed healthcare professionals were well aware that osteoporotic vertebrae could never be transformed into a 'metallic spine'. The companies believed that this educated audience would appreciate that treatment with a bisphosphonate could reduce the risk of further fractures as described in the text, but that treatment could not reduce this risk to zero or reverse osteoporotic deformities.

The Appeal Board should note that the image of the winged messenger was the Roman god, Mercury, not the Greek god Hermes, as asserted by Merck Sharp & Dohme. The purpose of using silver to show the passage of Mercury, the messenger of the gods, was consistent with the name of the god and the common name of the liquid metal mercury, namely: quicksilver.

During the development of this visual imagery, market research was conducted with physicians in the UK and other countries. The visual was tested first without the accompanying, qualifying text which appeared in the advertisement. The independent market research report showed:

1 the visual was 'understood and appreciated' by physicians; it evoked 'speed' and 'an osteoporotic spine';

2 the report contained no evidence to suggest that physicians viewed this visual as inferring an over-exaggeration of the product's attributes either in terms of magnitude of effect or a guarantee against further fractures;

3 with regard to communicating efficacy, the report specifically stated that 'even if efficacy is perceived, very few [physicians] … talk of the transformation from damaged osteoporotic bones into strong bones …. Physicians recognise an osteoporotic spine [and that the man] is racing into osteoporosis' and stood for improved health for a patient.

The companies were happy to share these market research findings with the Appeal Board, but requested that this confidential information was not distributed further.

The companies submitted that Case AUTH/972/1/00 provided a recent example of imagery being used to convey a message and not a measurable effect. This case concerned Merck Sharp & Dohme's challenge of Bayer's Lipobay 'Bound to Drop' claim, which was present on a visual containing an elephant trying to cross a tightrope. The Panel noted that the elephant would fall and the implication from the claim and the illustration was that Lipobay would always lower LDL-cholesterol. The Panel did not accept, however, that the audience would interpret the claim as guaranteeing that all patients prescribed Lipobay would experience a clinically significant fall in LDL-cholesterol. 'Bound to drop' was immediately followed, and qualified, by the claim 'New Lipobay 400mcg lowers LDL-cholesterol by up to 44%'. No breach of the Code was ruled. The companies believed that the interpretation here was significant and had parallels with this case, because the companies could not agree that sensible, informed healthcare professionals would interpret the Actonel visual as a guarantee of perfect bone and protection against the development of further vertebral fractures. No bone turned to metal.

Interestingly, Merck Sharp & Dohme's most recent advertisement for its product alendronate in the UK used artwork of a woman who appeared to have a healthy skeleton. Merck Sharp & Dohme appeared not only to be commercially mischievous by bringing this complaint but, more importantly, to be guilty of hypocrisy according to its own standards of portraying diseased bone and the effects of treatment.

In conclusion, the companies believed that the Actonel visual conveyed an impression of speed of action and efficacy, as the Panel noted. They did not believe that physicians interpreted this visual in terms of 'magnitude of effect' for the product. The companies therefore did not believe that the visual exaggerated or misled as to magnitude of response to treatment with Actonel.

APPEAL BOARD RULING

The Appeal Board noted the market research findings. The Appeal Board considered that the visual was a striking image designed to catch the reader's eye. It was not meant to be an anatomical representation of the effect of Actonel on the spine. The effect of Actonel on the spine was discussed in the text immediately adjacent to the illustration. The Appeal Board considered that healthcare professionals would be well aware of the effects of osteoporosis and that treatment delayed progression of the disease. The Appeal Board did not consider that the advertisement was misleading or exaggerated as alleged. No breach of Clauses 7.6 or 7.8 was ruled. The appeal was successful.

Complaint received **24 July 2000**

Case completed **12 October 2000**

CASE AUTH/1058/7/00

GENERAL PRACTITIONER v NOVARTIS

Stepwise campaign

A general practitioner complained about a newspaper advertisement and a booklet produced by Novartis. The advertisement was headed 'Fungal nail infection?' It referred the reader to a freephone number, a freepost address or a website for a free information booklet. The advertisement stated that it was sponsored by Novartis and included the phrase 'Stepwise your first step towards healthier looking nails'. The booklet, entitled 'Feet and Nails stamping out problems', discussed athlete's foot and fungal nail infections as well as tips about caring for feet and nails. The complainant noted that the advertisement appeared in the Daily Telegraph and that similar advertisements were placed in other newspapers and also appeared on television. In the complainant's view, the advertisement, taken in conjunction with the booklet, was a direct inducement to the public to seek prescription only medication, some of which was produced by the booklet's sponsor. Also, the booklet did not mention that there were perfectly adequate treatments available from pharmacies without prescription for athlete's foot. Nor did it state that fungal nail infection could be so trivial a complaint as to be not worth bothering about – rather it encouraged people to seek treatment. It was alleged that the advertisement and booklet were a sophisticated way of advertising prescription only medicines to the public. Further, the booklet might cause unnecessary worry and did not inform the public of effective OTC medicines.

The Panel noted that the Stepwise campaign had previously been the subject of complaints that it constituted the advertising of a prescription only medicine to the general public. A case in 1997 had gone to appeal and no breach of the Code had been ruled. Similar complaints since then had not been proceeded with because there was no new evidence or change in circumstances which raised doubts as to whether the same decision would be taken in respect of the subsequent complaints. The present complaint, however, also referred to the booklet causing unnecessary worry and not informing the public of effective OTC medicines. These aspects were taken up with Novartis as they had not previously been considered.

In relation to the allegation that the booklet might cause unnecessary worry, the Panel did not consider that the booklet was unacceptable. The phrases 'the fungus won't go away without treatment' and 'it was likely to get worse without treatment' were not unreasonable. No breach of the Code was ruled in that regard. The Panel noted that the booklet did not refer to the availability of treatments from the pharmacy. Novartis had submitted that there were no OTC treatments for fungal nail infection and that the booklet was made available via the advertisement which did not mention athlete's foot. The advertisement only referred to fungal nail infections. With regard to the treatment of athlete's foot, the booklet referred regular sufferers to their doctor but there was no reference to the fact that remedies could be bought at pharmacies. The Panel considered that the failure to mention that there were OTC products available for athlete's foot meant that the booklet was not balanced and therefore ruled a breach of the Code.

A general practitioner complained about an advertisement and a booklet produced by Novartis Pharmaceuticals UK Ltd. The advertisement was published in the Daily Telegraph on 4 July and was headed 'Fungal nail infection?'. It referred the reader to a freephone number, a freepost address or a website for a free information booklet. The advertisement stated that it was sponsored by Novartis and included the phrase 'Stepwise your first step towards healthier looking nails'. The booklet, entitled 'Feet and Nails stamping out problems' (ref STEP 1/99), discussed athlete's foot and fungal nail infections as well as tips about caring for feet and nails.

COMPLAINT

The complainant noted that the advertisement appeared in the Daily Telegraph and that similar advertisements were placed in other newspapers and also appeared on television.

In the complainant's view, the advertisement, taken in conjunction with the booklet, was a direct inducement to the public to seek prescription only medication, some of which was produced by the booklet's sponsor. Also, the booklet did not mention that there were perfectly adequate treatments available from pharmacies without prescription for athlete's foot. Nor did it state that fungal nail infection could be so trivial a complaint as to be not worth bothering about – rather it encouraged people to seek treatment – 'the fungus won't go away without treatment', 'it is likely to get worse without treatment' – both statements that might not be entirely true.

The complainant alleged that the advertisement and booklet were a sophisticated way of advertising prescription only medicines to the public. Further, the phrases in the booklet might cause unnecessary worry and did not inform the public of effective OTC medicines.

When writing to Novartis the Authority pointed out that the materials had already been the subject of complaints that they constituted advertising a prescription only medicine to the public. A case in 1997 (Case AUTH/516/3/97) had been the subject of appeal and no breach of Clauses 20.1 and 20.2 of the Code had been ruled. Subsequent similar complaints had not been proceeded with as there was no new evidence or change in circumstances which raised doubts as to whether the same decision would be made in respect of the subsequent complaints, the most recent of which had been received in January 2000. The decision not to proceed had been made in accordance with Paragraph 5.1 of the Code.

The complaint now to be considered, Case AUTH/1058/7/00, raised matters regarding the booklet causing unnecessary worry and not informing

the public of effective OTC medicines which had not been previously considered. These were taken up with Novartis.

RESPONSE

Novartis confirmed that the changes to the programme materials since the previous case in January 2000 were the development of new advertisements and the placing of the booklet text on the Internet. The booklets were the same as those provided to the Authority in January 2000. An additional booklet, STEP/7/00, had also been developed as a modification of STEP 3/99. The current stepwise campaign was relaunched in May/June 2000. The materials consisted of the advertisement and booklet (STEP 1/99) at issue, a leaflet headed 'Fungal nail infection?' (STEP 7/00), a leaflet headed 'Stamping out Athlete's foot' (STEP 2/99), a leaflet 'How to recognise problem toenails when you see them' (STEP 3/99) and a leaflet 'STEP Check' (STEP 6/99).

The differences between the relaunched campaign and the campaign complained about in January 2000 was that the campaign was now sponsored by Novartis (instead of Sandoz), the freepost address had changed and all references to the word cured in the context of treatment of foot and nail infections had been removed.

With regard to the allegation that phrases in the booklet might cause unnecessary worry, Novartis stated that the claims 'The fungus won't go away without treatment' and 'it is likely to get worse without treatment' were, in the context of fungal nail infection, accurate and factual. Spontaneous resolution of fungal nail infection was not a realistic proposition nor was it likely that, once infected, the nail would fail to deteriorate if not treated appropriately (Roberts 1993 and Denning *et al* 1995).

It should be remembered that by the time the patient received this booklet they would have already identified what they believed to be a fungal nail infection and were seeking advice and guidance on how to manage it. They might well have noted for themselves a progression of their athlete's foot or noted a gradual deterioration of their nails as the infection spread and they changed colour and crumbled. This progression was clearly described at the beginning of the booklet in the section 'How do I know that I've got it?'.

The Stepwise Programme was based on research indicating that there was a large untreated reservoir of patients in the community who did not recognise that they had a fungal infection or who had received ineffective therapy in the past which had led them to consider their condition untreatable. Fungal nail infection was thought to affect over a million patients in the UK at any one time, with an estimated 200,000 new patients each year. An analysis of such patients had shown that, as with athlete's foot, only a small percentage of patients with fungal nail infection sought professional advice, although 80% felt that they would have done so if they had realised that they were suffering from a treatable fungal infection (Roberts 1992).

With regard to the complainant's view that fungal nail infection could be so trivial a complaint as to be not worth bothering about, Novartis submitted that although fungal infections of the nails were sometimes disregarded as superficial or cosmetic, it would be wrong to underestimate the implications of fungal nail infection to the patient or the eventual consequences of onychomycosis which could become unsightly, embarrassing and occasionally disabling (Scher (1996 and 1994), Drake (1998), Moore (1994), Carroll (1993) and Owen (1999)). It was clear that patients themselves did not consider this condition trivial or they would not feel prompted to find out more about the Stepwise programme.

Novartis would not agree that these statements were 'worrying' to patients, having been included in the materials since 1995 and subject to extensive review by the Medicines Control Agency, the Panel and the Code of Practice Appeal Board. In addition, the booklets had been very well received by the public in the five years since their introduction with no complaints or comments received in relation to any worrying or alarmist content.

With regard to the allegation that the material did not inform the public of effective OTC medicines, Novartis submitted that it was important to note that none of the products currently licensed for the treatment of fungal nail infection were currently available OTC. In relation to athlete's foot, the booklet in question was designed to be sent out following a patient's positive response to the fungal nail infection advertisement. Novartis agreed that the emphasis of the booklet was on good foot hygiene and techniques for avoiding infection. In the case of athlete's foot, which was thought to affect from 10-15% of the UK population, the lack of adequate advice on good foot hygiene was often cited as an issue in a population of patients in which only a quarter would have discussed their condition with their doctor. Whilst specific medicines were not referred to anywhere in the booklet, the section 'How do I treat it' gave patients some clear guidance on what they could do for themselves to manage athlete's foot. Only the regular sufferer was advised to seek their doctor's advice, on the assumption that having classified themselves as a 'regular sufferer', they would have identified that the treatments they had been using thus far have been suboptimal.

In conclusion, Novartis was confident that the Stepwise Programme materials were factual and balanced and continued to offer valuable advice and support to patients who believed that they might have a fungal infection of their feet or nails.

PANEL RULING

The Panel noted that the Stepwise campaign had been relaunched in May/June 2000. The advertisement the subject of the current complaint was different to the original advertisement. The original advertisement was headed 'There is no disguising problem toenails' followed by a picture of a big toe wearing a pair of glasses, with a nose and moustache. The words beneath the illustration were 'Thick brittle discoloured toenails may be caused by a fungal infection. For a

free leaflet and advice on how they can be cured write to …' followed by a freepost address. A freephone number was also given. The advertisement included a logo 'Your first step towards healthier looking nails. Stepwise sponsored by Sandoz'. The new advertisement was headed 'Fungal nail infection?' Followed by a picture of a big toe. The advertisement stated 'Cut it out!' over the illustration of the toenail. This was followed by 'Thick brittle, discoloured nails could be caused by a fungal nail infection that may spread to other people. For an information booklet write to [followed by a freepost address, a freephone number] or visit our Website – and take the first step towards healthier nails.' The same logo appeared on the new advertisement except that it stated that Stepwise was sponsored by Novartis.

The booklet (STEP 1/99), also complained about, was only very slightly different to the one previously considered. It was now sponsored by Novartis, it had a new freepost address and all references to the word cured in the context of treatment of foot and nail infections had been removed.

The Director considered that with regard to the allegation regarding the promotion of a prescription only medicine to the general public, there was no new evidence and nor had the passage of time or a change of circumstances raised doubts as to whether the same decision would be reached in respect of the current complaint which related to the advertisement in conjunction with the booklet. In accordance with Paragraph 5.1 of the Constitution and Procedure the Director decided not to proceed with this aspect of the complaint.

The Panel noted the requirements of Clause 20.2 of the Code that information made available to the general public must 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.

The Panel considered the allegation that the booklet might cause unnecessary worry. It did not consider that the booklet was unacceptable. The phrases 'the fungus won't go away without treatment' and 'it was likely to get worse without treatment' were not unreasonable. No breach of Clause 20.2 of the Code was ruled.

The Panel noted that the booklet did not refer to the availability of treatments from the pharmacy. The Panel noted Novartis' submission that there were no OTC treatments for fungal nail infection and that the booklet was made available via the advertisement which did not mention athlete's foot. Further, the advertisement only referred to fungal nail infections. With regard to the treatment of athlete's foot the booklet referred regular sufferers to their doctor but there was no reference to the fact that remedies could be bought at pharmacies. The Panel considered that the failure to mention that there were OTC products available for athlete's foot meant that the booklet was not balanced. The Panel therefore ruled a breach of Clause 20.2 of the Code.

The Panel noted that the leaflet STEP 7/00 and the website had been launched in May/June. They had not been considered in the previous complaints. Neither the leaflet STEP 7/00 nor the website were the subject of the current complaint.

Complaint received **28 July 2000**

Case completed **16 October 2000**

CASE AUTH/1059/8/00

ANONYMOUS PATIENT v WYETH

Meeting, wine tasting and social evening

A patient complained anonymously about a poster on display at a hospital by which the doctors' mess advertised a free wine tasting. The poster said that this was sponsored by Lederle plus free Chinese take-away. Then on to a public house and then a nightclub. The poster featured a picture of two mice, one holding a glass of wine, standing behind a piece of cheese. The complainant asked whether this was the type of encouragement companies used to persuade doctors to prescribe their products.

The Panel considered that the poster gave the impression that the meeting was for social purposes only and that it was organised and paid for by Lederle. It gave no indication of any medical or educational content. The Panel noted from Wyeth's submission that the meeting comprised a presentation and discussion of treatment options for reflux oesophagitis, gastritis and *Helicobacter pylori* eradication and lasted from 7.30pm to 9.00pm. The meeting had been arranged with the mess president who had arranged for the posters. Wyeth had submitted that its representative had been unaware of the poster until he attended for the meeting and that the wine tasting and the visits to a public house and a nightclub were not part of his arrangements.

The Panel was concerned about the overall arrangements for the meeting and the impression given by the poster. Whilst the representative had no prior knowledge of the poster, it appeared to be the usual practice of the mess president to supply posters to advertise such meetings. The Panel considered that when a meeting was arranged the representative ought to ensure at the outset that the respective roles and responsibilities of all parties involved were discussed and agreed and were in accordance with the Code.

The Panel considered that the level of hospitality provided was not appropriate. The overall cost of around £20 per head was not unreasonable but the amount of alcohol provided (13 bottles of wine and 24 bottles of beer) was excessive given there were 15 delegates, and out of proportion to the occasion. A breach of the Code was ruled. On balance however, given the particular circumstances of this case, the Panel did not consider that the representative had failed to maintain a high standard of ethical conduct. No breach of the Code was ruled in that regard and nor did the Panel consider that these particular circumstances meant that the company had failed to maintain high standards or had brought discredit upon or reduced confidence in the pharmaceutical industry.

An anonymous complainant who described himself as a patient at a named hospital complained about a poster on display at the hospital. The poster read 'The doctors mess presents. Free wine tasting. Thursday 18 May 2000. Sponsored by Lederle plus free Chinese takeaway. Then onto [a named public house] followed by [a named nightclub]. Miss it and miss out!!!' The poster featured a picture of two mice, one holding a glass of wine, standing behind a piece of cheese.

COMPLAINT

The complainant asked whether this was the type of encouragement that drug companies used to persuade doctors to prescribe their products.

RESPONSE

Wyeth stated that its representative organised a medical meeting for junior doctors at the hospital on 18 May. The meeting started at 7.30pm and took the format of a presentation on, and discussion of, treatment options for reflux oesophagitis, gastritis and *Helicobacter pylori* eradication. This was followed by individual discussion on the issues presented between the representative and the doctors. The representative's meeting concluded around 9pm.

In association with this meeting, Wyeth's representative organised hospitality in the form of Chinese takeaway food, modest table wine and beer. The total cost for the food and beverages was £284.73 (around £20 per head). Copies of receipts were provided.

The meeting was held in the junior doctors' mess at the hospital and Wyeth's representative made arrangements for the meeting to be held at this venue through a medical senior house officer at the hospital who was also the mess president. Wyeth's representative invited junior doctors at the hospital personally.

Without the knowledge of Wyeth's representative, the mess president independently organised a junior doctors social evening to follow the meeting and decided independently to organise a poster to promote her arrangements; this was the poster at issue.

The poster was placed on the noticeboard on the inside of the junior doctors' mess door (an area that was not accessible to patients or the general public and away from the main public areas of the hospital). Wyeth's representative had no prior warning of the content of this notice until he saw it for the first time when he attended for his meeting on the evening of 18 May.

Wine tasting and a trip to a local public house and nightclub did not form part of the meeting that had been organised by Wyeth's representative and he did not sponsor them. Wyeth's representative had no knowledge that his meeting had been linked to a wine tasting evening or to these activities until he saw the poster on the evening of 18 May.

As indicated above, the poster did not reflect the meeting arranged by Wyeth's representative, but rather the mess president's view of an evening she proposed on the back of the Wyeth's representative's presentation.

Accordingly, the poster misrepresented the true nature of the meeting that had been organised by Wyeth's representative. Unfortunately, this had led the complainant to assume that improper encouragement was being offered by a pharmaceutical company to persuade doctors to prescribe its products when in fact this was not so.

Wyeth's representative had passed the ABPI examination. Wyeth provided a copy of the instructions issued to its representatives regarding meetings. These were set out in Wyeth's Field Force Instructions in relation to the Code, a copy of which was provided.

Wyeth also provided a copy of a letter from the mess president confirming her role in organising the events that took place that evening as well as the role and knowledge of the Wyeth representative. She stated that in her position as mess president between August 1999 and August 2000, she arranged numerous meetings between junior doctors and pharmaceutical companies. She arranged such a meeting on Thursday, 18 May. As usual, she supplied the posters to advertise the meeting which were not seen by the Wyeth representative prior to the meeting. The format of the meeting was a short presentation followed by wine or soft drinks. The rest of the evening was organised by her as a mess outing and did not involve any pharmaceutical company.

Wyeth submitted that there had been no breach of Clauses 2, 9.1, 15.3 or 19 of the Code by the company or its representative. Specifically, there had been no breach of Clause 2 in that the activities organised by Wyeth's representative (a medical meeting involving a presentation and follow on discussion together with associated hospitality) were organised in accordance with the Code of Practice guidelines for such meetings and were not of a nature such to bring discredit upon, or to reduce confidence in, the pharmaceutical industry.

There had been no breach of Clause 9.1 in that the activities organised by Wyeth's representative did recognise the special nature of medicines and the professional standing of the audience to which they were directed, and there had been no breach of Clauses 15.3 and 19.1 in that the hospitality provided at the meeting organised by Wyeth's representative was secondary to the true nature of the meeting as represented by its representative to the doctors he had invited – a medical presentation and discussion. The poster was prepared independently of Wyeth's representative and without his knowledge misrepresented the true nature of the meeting.

PANEL RULING

The Panel examined the text and layout of the poster. There was no indication of any medical or educational content to the meeting and no specific reference made to the presentation to be given. The Panel considered that the poster gave the impression that the meeting was for social purposes only and that it was organised and paid for by Lederle.

The Panel noted Clause 19 and its supplementary information which stated that meetings must have a clear educational content. Companies were permitted to provide appropriate hospitality to health professionals in association with such meetings. Hospitality had to be secondary to the purpose of the meeting, the level must be appropriate and not out of proportion to the occasion and the costs must not exceed that level which the recipients would normally adopt when paying for themselves. Meetings which were wholly or mainly of a social or sporting nature were unacceptable. The impression created by the arrangements must always be kept in mind.

The Panel noted from Wyeth's submission that the meeting comprised a presentation and discussion of treatment options for reflux oesophagitis, gastritis and *Helicobacter pylori* eradication and lasted from 7.30 to 9pm. It was unclear whether the food and alcohol were consumed during or after the $1^1/_2$ hour meeting. The Panel examined the receipts and noted that expenditure, excluding disposable cutlery, of £284.73 had been incurred for 15 people. The Panel noted that 13 bottles of wine had been purchased together with 24 bottles of beer. The Panel considered that the amount of alcohol provided was excessive given the nature of the meeting and the estimated number of delegates.

The Panel noted that the meeting was arranged with the mess president who had provided a letter explaining her role. The Panel noted that there were some differences between the parties' accounts. The company stated that the representative invited junior doctors personally to the meeting whilst the mess president referred to arranging meetings between doctors and pharmaceutical companies and stated that 'as usual, I supplied the posters to advertise the meeting'. The meeting was referred to by the mess president as a short presentation followed by wine or soft drinks. The company stated that it lasted for $1^1/_2$ hours. The Panel noted that receipts in respect of soft drinks had not been provided. The mess president did not mention the Chinese takeaway in her letter.

The Panel was concerned about the overall arrangements for the meeting. The Panel noted that whilst the representative had no prior knowledge of the poster, it appeared to be the usual practice of the mess president to supply posters to advertise such meetings. The Panel considered that when meetings were arranged the company ought to ensure at the outset that the respective roles and responsibilities of all parties involved were discussed and agreed and were in accordance with the Code. The Panel considered that the usual practice of a third party such as the mess president ought to be ascertained at this stage. The Panel noted however that Wyeth's representatives' briefing material was silent on this point. Further the Panel did not know what discussions had taken place when the meeting was arranged.

The Panel was concerned about the overall arrangements for the meeting and the impression given particularly by the poster. The Panel noted the submission from Wyeth that the representative had had nothing to do with the poster.

The Panel considered that the level of hospitality provided was not appropriate. The overall cost of

around £20 per head was not unreasonable but the amount of alcohol provided was excessive given the number of delegates and out of proportion to the occasion. A breach of Clause 19.1 was ruled.

On balance however, given the particular circumstances of this case, the Panel did not consider that the representative had failed to maintain a high standard of ethical conduct. No breach of Clause 15.2 was ruled. Neither did the Panel consider that these particular circumstances meant that the company had failed to maintain high standards or brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clauses 2 and 9.1 was ruled.

Complaint received **1 August 2000**

Case completed **25 September 2000**

CASE AUTH/1060/8/00

GENERAL PRACTITIONER v ASTRAZENECA

Conduct of representative

A general practitioner complained about the conduct of a representative from AstraZeneca. The representative had come to see the complainant at his surgery but had been politely told that he did not see representatives on Wednesday or Friday. When told no, the complainant alleged that the representative had tried to bribe him by saying that he had called to deliver something. The complainant asked the representative to keep what he had to deliver and to make an appointment to see him another time. In spite of that the representative insisted on seeing the complainant and sent his card in again with a hand written note saying 'that I would like to deliver something that I have brought to you'. The representative was told that if he insisted on seeing the complainant, he would be reported to the company and to the Authority. If he had brought something for the complainant he should leave it with the receptionist. However, he had just left a pen. He had not delivered what he had come to deliver.

The Panel noted that according to the complainant the representative had been told that he did not see representatives on Wednesday or Friday. At this point the representative had said that he had called to deliver something. The complainant had asked the representative to keep what he had to deliver and to make an appointment for another time. According to the company, the representative had asked to see the complainant and had been told to call back another day. The representative then asked the receptionist if she would ask the complainant if he would see him and mentioned that he had a pen or a shoulder bag for him. These details were put on the back of a business card which the receptionist took in to the complainant. The Panel noted that the representative had left a pen for the complainant before leaving the surgery. The Panel considered that by referring to the promotional aids after he had been told that the complainant did not see representatives on Wednesdays or Fridays and to call back, the representative had used the promotional aids as an inducement to gain an interview. A pen had been left by the representative but nevertheless the promotional aids had been offered as a reason for the complainant to see the representative. This was unacceptable and a breach of the Code was ruled. The representative had failed to maintain a high standard of ethical conduct and the Panel therefore also ruled a breach in that regard.

A general practitioner complained about the conduct of a representative from AstraZeneca UK Limited. The letter of complaint had been sent to AstraZeneca and copied to the Authority.

COMPLAINT

The representative had come to see the complainant at his surgery but had been politely told that he did not see representatives on Wednesday or Friday. When told no, the complainant alleged that the representative had tried to bribe the complainant by saying that he had called to deliver something. The complainant asked the representative to keep what he had to deliver and to make an appointment to see him another time. In spite of that the representative insisted on seeing the complainant and sent his card in again with a hand written note saying 'that I would like to deliver something that I have brought to you'. That was not the thing to do as the complainant did not see representatives on a Wednesday or a Friday and he was also very busy.

The representative was told of the consequences if he insisted on seeing the complainant. He would be reported to the company and to the Authority. If he had brought something for the complainant he should leave it with the receptionist. However, he had just left a pen for which the complainant was grateful. He had not delivered what he had come to deliver and had attempted to bribe the complainant by telling his staff that he had something to deliver.

RESPONSE

AstraZeneca stated that the representative in question was relatively new to the pharmaceutical industry. He joined a contract organisation on 26 May of this year and had been employed as a medical representative by AstraZeneca, on a contract basis, to cover maternity leave. He had not yet sat the ABPI examination. He had received Code of Practice training on a one-to-one basis from his AstraZeneca manager who had been in the industry for many years and was experienced in Code of Practice training.

The representative had been interviewed by his manager and AstraZeneca understood the facts to be as follows. The representative had called at the complainant's surgery for the first time with the intention of promoting AstraZeneca's range of respiratory products and discussing possible support which could be given to the practice's asthma clinic. On arrival, the representative spoke to the receptionist, gave her some notepads and pens, and asked if he could see the complainant. The receptionist replied to the effect that the complainant did not usually see representatives and that he should call back another day. The representative asked the receptionist if she would consider asking the complainant if he would see him and mentioned that he had a pen or a shoulder bag for him. The receptionist asked the representative for his card and said she would go in and speak to the complainant. The representative hastily wrote a note on the back of his business card, mentioning the promotional aids which he had brought, and the receptionist took it in to the complainant. When she returned, she told the representative that if he did not leave what was meant for the complainant, he would report him. The representative was shocked at this reaction, took the pen which he had brought, attached it to his card and gave it to the receptionist who took it in to the complainant. When she returned, the representative asked her if the complainant would see him or consider giving him a future appointment. The receptionist told the representative that the complainant did not want to see him. Since the representative's reception at the surgery had been less than friendly, he immediately left, apologising to the receptionist.

When AstraZeneca received the complaint, the representative's manager telephoned the complainant to discuss the matter and apologise for the representative's perceived persistence. AstraZeneca understood that the complainant accepted the apology and agreed that that would be the end of the matter. The representative had since been questioned by his manager about the circumstances surrounding his offer of promotional aids to the complainant. The representative offered a pen or a shoulder bag. At the time, he mistakenly believed that the Code did not allow gifts totalling more than £5. He therefore believed that he could not give both items and so offered a choice of one or the other. When asked at the surgery to leave what he had brought, he left only one item, the pen, which he believed was the correct thing to do.

The promotional materials at issue in this case were a ball-point pen branded 'Oxis 12' and a shoulder bag for documents branded 'Pulmicort'. Each item cost no more than £5 and was of the type of promotional aid routinely provided to doctors by pharmaceutical representatives in the course of their business. AstraZeneca submitted that these were of a proper standard and therefore denied any breach of Clause 9.1.

From the accounts given concerning the representative's visit to the surgery, AstraZeneca believed that the representative behaved in a proper and ethical manner. He did not see the complainant. His only dealings were with the receptionist and he did as instructed by her during the period of his visit. There was no suggestion that he did otherwise. AstraZeneca therefore denied any breach of Clause 15.2.

Again, from the accounts given on the matter of the promotional aids, AstraZeneca believed that the representative had acted correctly according to his understanding of the requirements of the Code. He provided the receptionist with some promotional aids and made an offer of a choice of promotional aids to the complainant at the time of asking for an interview with him. He did not make the offer conditional on his seeing the complainant, nor was there any suggestion that he did make the offer conditional or imply that it was so. When asked to leave what he had brought, he left the pen. Unfortunately, the representative believed that the Code allowed him to offer gifts up to the value of £5 in total, which was why he offered one item, a pen or a bag, and left only one item when refused an interview. Had the representative correctly understood that he could have given several items, each to a value up to £5, and had left both the pen and bag, perhaps the perception of his actions at the surgery might have been different. Notwithstanding the representative's understanding of the Code, he offered one item and left one item. He did not use the gift of a promotional aid as a condition for an interview. AstraZeneca therefore denied any breach of Clause 15.3.

As stated previously, the representative was new to the area. He was calling at the surgery for the first time and was unaware of the arrangements for seeing representatives. Towards the end of the discussion, when told by the receptionist that the complainant did not want to see him, he left immediately and did not attempt to see him by another means. The representative had had no further contact with the surgery since that day. AstraZeneca submitted that the representative respected the wishes of the complainant and therefore denied any breach of Clause 15.4.

Whilst it was most unfortunate and regrettable that the complainant had been moved to complain about the representative's visit to his surgery, AstraZeneca did not believe that the events which transpired on that day were such as to bring discredit upon or reduce confidence in the pharmaceutical industry. AstraZeneca emphasised that when the representative's manager telephoned the complainant to discuss the matter, the complainant was satisfied with a verbal apology and agreed that the matter was at an end. AstraZeneca therefore denied any breach of Clause 2.

PANEL RULING

The Panel noted that the representative had asked the receptionist if he could see the complainant. According to the complainant the representative had been told that the complainant did not see representatives on Wednesday or Friday. At this point the representative had said that he had called to deliver something. The complainant had asked the representative to keep what he had to deliver and to

make an appointment for another time. According to the company the representative had asked to see the complainant and had been told to call back another day. The representative then asked the receptionist if she would ask the complainant if he would see him and mentioned that he had a pen or a shoulder bag for him. These details were put on the back of a business card which the receptionist took in to the complainant. The Panel noted that the representative had left a pen for the complainant before leaving the surgery.

The Panel noted that Clause 15.3 stated that representatives must not employ any inducement or subterfuge to gain an interview. The Panel considered that by referring to the promotional aids after the representative had been told that the complainant did not see representatives on Wednesdays or Fridays and to call back, the representative had used the promotional aids as an inducement to gain an interview. The Panel noted that a pen had been left by the representative but nevertheless the promotional aids had been offered as a reason for the complainant to see the representative. This was unacceptable and a breach of Clause 15.3 of the Code was ruled. The representative had failed to maintain a high standard of ethical conduct. The Panel therefore ruled a breach of Clause 15.2.

The Panel did not accept that the circumstances warranted a breach of Clause 2 of the Code which was used as a sign of particular censure. No breach of that clause was ruled. The Panel did not accept that there had been breaches of Clauses 9.1 and 15.4 and thus ruled no breach of those clauses.

Complaint received **3 August 2000**

Case completed **28 September 2000**

CASE AUTH/1064/8/00

SANOFI-SYNTHÉLABO v LUNDBECK

Sonata detail aid

Sanofi-Synthélabo complained about a detail aid for Sonata (zaleplon) issued by Lundbeck. Sanofi-Synthélabo supplied Stilnoct (zolpidem). A page headed 'Sonata 10mg allows patients to function even if administered during the night' included a graph headed 'Memory function 4 hours after dose administered n=36'. The graph compared Sonata 10mg with placebo and zolpidem 10mg with regard to a memory test relating to the number of words correctly recalled (delayed); after four hours the results for placebo and Sonata were the same. There were statistically significant differences between Sonata and zolpidem ($p<0.001$) and zolpidem and placebo ($p<0.001$). Sanofi-Synthélabo alleged that the material represented by this graph was not balanced, fair or objective because zaleplon could be taken up to four hours before rising whist zolpidem should not be taken unless seven to eight hours remained for uninterrupted sleep. The graph sought to create the impression that zolpidem led to residual effects that might impair next day psychomotor performance whilst zaleplon did not. The appropriate comparison would have been one comparing the effects of zaleplon four hours post dosing with the effects of zolpidem eight hours post dosing.

The Panel noted that the Stilnoct summary of product characteristics (SPC) said that to reduce the risk of anterograde amnesia patients should ensure that they would be able to have an uninterrupted sleep of 7-8 hours. The Sonata SPC said that to reduce the risk of anterograde amnesia patients should ensure that they would be able to have uninterrupted sleep of four hours or more after taking Sonata. A previous page of the detail aid headed 'Sonata 10mg offers a 'true' flexible dosing regimen' compared the dosing regimen of Sonata, which could be taken at bedtime or as long as there were four hours of sleep remaining, with zolpidem, which should be taken when the patient was able to have 7-8 hours of uninterrupted sleep, and zopidone which should only be taken when the patient was able to have a full night's sleep.

The Panel noted the differences between the two products. It considered that the fact that Sonata could be taken when four hours of uninterrupted sleep remained could be relevant when deciding which of the products to prescribe. The Panel noted Lundbeck's submission that there was no specific statement in the posology section of either the Sonata or Stilnoct SPCs regarding a time limit for taking the medication in relation to expected awakening. The time limit related to the incidence of anterograde amnesia. The Panel considered the time recommendations in the SPC were relevant when presenting comparative data on memory function. The page in question showed data for Sonata which had been administered in accordance with the recommendation in its SPC, zolpidem had not. The material had referred to the dosing regimen on a previous page but did not link the time requirement with amnesia. The Panel considered that the page in question was unfair in that differences between the products with regard to the time of administration and its effect on retrograde amnesia had not been made clear when presenting data on memory impairment. The Panel ruled a breach of the Code.

Sanofi Synthélabo complained about a detail aid (ref: 0100/SON/525/001 (242)) for Sonata (zaleplon) issued by Lundbeck Ltd. Sanofi-Synthélabo supplied Stilnoct (zolpidem).

Page 5 headed 'Sonata 10mg allows patients to function even if administered during the night'

included a graph headed 'Memory function 4 hours after dose administered n=36'. The graph compared Sonata 10mg with placebo and zolpidem 10mg with regard to a memory test relating to the number of words correctly recalled (delayed); after four hours the results for placebo and Sonata were the same. There were statistically significant differences between Sonata and zolpidem ($p<0.001$) and zolpidem and placebo ($p<0.001$).

COMPLAINT

Sanofi-Synthélabo stated that it had been engaged in correspondence over a number of issues relating to this promotional item and had been able to resolve most. However, it had been unable to obtain a satisfactory response over one outstanding matter relating to the use of the prominently displayed graph which compared memory impairment with zaleplon, placebo and zolpidem four hours after dosing. Sanofi-Synthélabo contended that the material represented by this graph was not balanced, fair or objective and a breach of Clause 7.2 of the Code was alleged. The reasons for this assertion were that zaleplon could be taken up to four hours before rising whilst zolpidem should not be taken unless seven to eight hours remained for uninterrupted sleep. The graph sought to create the impression that zolpidem led to residual effects that might impair next day psychomotor performance whilst zaleplon did not. The appropriate comparison would have been one comparing the effects of zaleplon four hours post dosing with the effects of zolpidem eight hours post dosing.

RESPONSE

Lundbeck stated that the page illustrated results from a study by Danjou *et al* entitled 'A comparison of the residual effects of zaleplon and zolpidem following administration 5 to 2h before awakening'.

Sonata was licensed for the treatment of patients with insomnia who had difficulty falling asleep. The pharmacokinetic and pharmacodynamic properties of the compound (Sonata was rapidly absorbed when administered orally with peak plasma concentrations at approximately one hour and an elimination half-life of approximately one hour) allowed the patient to take the medication either prior to going to bed or after the patient had gone to bed and was experiencing difficulty falling asleep. The recommendation was that if the latter practice was adopted at least four hours of 'sleep time' should be remaining.

The study demonstrated the lack of any residual hypnotic or sedative effects when zaleplon 10mg was administered as little as two hours before waking in normal subjects. As was usual in these studies, besides a placebo a comparator was also used. As there were only two marketed non-benzodiazepine hypnotics (zolpidem and zopiclone) it was reasonable to use one of these as a comparator. For reasons outlined in the study ie binding to the same neuroreceptor (BZD1), and studies considering zolpidem to be essentially free of residual effects (Langtry *et al*, Undén *et al*) all suggested that it was a stringent and fair comparator at its currently recommended dose of 10mg.

Lundbeck submitted that it was important for both prescribers and patients to be confident that if Sonata was taken appropriately they would be able to function normally upon awakening (four hours post dosing) and this was adequately demonstrated by the study. To measure residual effects beyond the time parameters in this study would have yielded no useful data towards answering that question.

Of note there was no specific statement in the posology section of either the Sonata or Stilnoct summaries of product characteristics (SPCs) as to a time limit for taking of the medication in relation to expected awakening (ie four hours or seven to eight hours respectively). Similarly there were no specific timelines, as above, that were included in the patient information leaflets for either product. Lundbeck was also aware that patients might not comply with administration recommendations for a number of reasons. Patients often did not have an adequate period of time in which to sleep (eg shift workers), might have to suddenly wake up in the night (eg children or other family member needing attention) or might take medication, inappropriately, when they could not achieve sleep. This could mean that medication might therefore result in residual symptoms when the patient had to subsequently get up.

Lundbeck submitted that the results for zaleplon from the study would give some assurance of a patient being able to function adequately even under these circumstances, especially as the authors noted that patients might have impaired psychomotor function without even being aware of it (a possible hazard if driving etc). It was responsible, therefore, that prescribers be made aware of such available data.

The results from the study by Danjou *et al* had been accurately represented and to have left out the results of the comparator, zolpidem, would have been inappropriate. Furthermore the graphs and bullet points all carried the appropriate time of administration (four hours) which was clearly marked and Lundbeck did not accept that any attempt had been made to mislead. Indeed no specific reference was made in the written text to zolpidem, but the statements had instead concentrated on the comparison between zaleplon and placebo.

In conclusion, therefore, Lundbeck denied any breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the Stilnoct SPC in the section headed 'Special warnings and precautions for use' and subheaded 'Amnesia' stated that to reduce the risk of anterograde amnesia patients should ensure that they would be able to have an uninterrupted sleep of 7-8 hours. The Sonata SPC stated in the section headed 'Special warnings and special precautions for use' and subheaded 'Amnesia' that to reduce the risk of anterograde amnesia patients should ensure that they would be able to have uninterrupted sleep of four hours or more after taking Sonata.

The Panel noted that page 3 of the piece headed 'Sonata 10mg offers a 'true' flexible dosing regimen' compared the dosing regimen of Sonata, which could be taken at bedtime or as long as there were four hours sleep remaining, with zolpidem, which should be taken when the patient was able to have 7-8 hours of uninterrupted sleep, and zopidone, which should only be taken when the patient was able to have a full night's sleep.

The Panel noted that Danjou *et al* compared the residual effects of zaleplon 10mg and zolpidem 10mg following administration 5, 4, 3 or 2 hours before morning awakening. The total time allowed for sleep was eight hours. The study authors noted that residual effects were mainly determined by pharmacodynamic factors, particularly the rate of absorption and distribution of the active medicine, its metabolic rate and terminal half life. Healthy volunteers had been used to avoiding the confounding effects of insomnia on morning psychomotor tests.

The Panel noted the differences between the two products. It considered that the fact that Sonata could be taken when four hours of uninterrupted sleep remained could be relevant when deciding which of the products to prescribe. The Panel noted the submission that there was no specific statement in the posology section of either Sonata or Stilnoct SPCs regarding a time limit for taking the medication in relation to expected awakening. The time limit related to the incidence of anterograde amnesia. The Panel considered the time recommendations in the SPC were relevant when presenting comparative data on memory function. The page in question showed data for Sonata which had been administered in accordance with the recommendation in its SPC, zolpidem had not. The material had referred to the dosing regimen on a previous page but did not link the time requirement with amnesia. The Panel considered that the page in question was unfair in that differences between the products with regard to the time of administration and its effect on retrograde amnesia had not been made clear when presenting data on memory impairment. The Panel ruled a breach of Clause 7.2 of the Code.

During its consideration of this case, the Panel noted that Danjou study was carried out on healthy volunteers with no history of insomnia to avoid the confounding effects of insomnia on morning psychomotor tests. This had not been mentioned on the graph nor on the page in question. The study authors concluded that Sonata was a hypnotic 'free of residual effects, at least in normal volunteers'. The Panel noted the supplementary information to Clause 7.2 of the Code that care must be taken with the use of healthy volunteer data so as not to mislead as to its significance. The Panel was concerned that the presentation of the healthy volunteer data was not in accordance with Clause 7.2 of the Code. The Panel requested that Lundbeck be advised of its views.

Complaint received **9 August 2000**

Case completed **3 October 2000**

CASE AUTH/1065/8/00

PHARMACIA & UPJOHN v SANOFI-SYNTHÉLABO

Promotion of Ditropan XL

Pharmacia & Upjohn complained about a cost comparison chart for Ditropan XL (oxybutynin) which appeared in a leaflet and a detail aid issued by Sanofi-Synthélabo. The cost comparison was in the form of a bar chart which compared the cost per day of Ditropan XL 5mg od (31.5p), Ditropan 5mg bd (45p), Ditropan XL 10mg od (63p) and tolterodine 2mg bd (109p). Tolterodine (Detrusitol) was Pharmacia & Upjohn's product.

Pharmacia & Upjohn stated that the chart suggested that the daily cost of treatment with tolterodine was significantly greater than with Ditropan XL. The licensed therapeutic dose of tolterodine (2mg bd) was unfairly compared with two low doses of Ditropan XL. The therapeutic range for Ditropan XL was 5-30mg od. In the pivotal study quoted earlier in the same mailing, Anderson *et al* (1999), the proportion of patients receiving doses ≥15mg daily was 61% in the per protocol population and 70% in the ITT population. Any formal comparison, other than using the licensed therapeutic range, was misleading in the absence of data from a head-to-head trial in which dose equivalence was properly evaluated.

The Panel noted from the Detrusitol summary of product characteristics (SPC) that its recommended dose was 2mg bd. The dose was reduced to 1mg bd in patients with impaired liver function and in the event of troublesome side effects the dose might be reduced to 1mg bd. According to its SPC the recommended dose for Ditropan XL was 5mg od which might be increased by 5mg a week to achieve a balance of efficacy and tolerability (up to a maximum of 30mg/day). The Panel noted the submission of Sanofi-Synthélabo that 91% of patients were treated with doses of Ditropan of 10mg daily or less. The Panel further noted that the Ditropan XL SPC stated that those taking immediate release oxybutynin could be switched to the nearest equivalent total daily dose of Ditropan XL. There was no direct comparative efficacy evidence for Ditropan XL and Detrusitol. A study by Malone-Lee *et al* 1998 concluded that tolterodine 2mg bd proved equally efficacious to oxybutynin 5mg bd but seemed to be associated with less side effects, particularly dry mouth. There was no claim for equivalent efficacy but the chart might be seen to imply that there was direct evidence of equivalent efficacy. The Panel noted that the most commonly prescribed doses of each medicine had been presented but this had not been made clear. A breach of the Code was ruled.

Pharmacia & Upjohn Limited submitted a complaint about the promotion of Ditropan XL (oxybutynin) by Sanofi-Synthélabo. The complaint concerned a cost comparison chart which appeared in two promotional items; a leaflet (ref: DIT00/014) which was used both as a mailing and GP detail aid and a hospital detail aid (ref: DIT00/013).

The cost comparison was in the form of a bar chart which compared the cost per day of Ditropan XL 5mg od (31.5p), Ditropan 5mg bd (45p), Ditropan XL 10mg od (63p) and tolterodine 2mg bd (109p). Tolterodine (Detrusitol) was Pharmacia & Upjohn's product. The chart was referenced to MIMS June 2000.

COMPLAINT

Pharmacia & Upjohn alleged that the cost comparison chart breached Clause 7.2. It suggested that the daily cost of treatment with tolterodine was significantly greater than with Ditropan XL. The licensed therapeutic dose of tolterodine (2mg bd) was unfairly compared with two low doses of Ditropan XL. The therapeutic range for Ditropan XL was 5-30mg od. In the pivotal study quoted earlier in the same mailing, Anderson *et al* (1999), the proportion of patients receiving doses ≥15mg daily was 61% in the per protocol population (Figure 3, n = 28/46) and 70% in the ITT population (Figure 4, n = 37/53).

Pharmacia & Upjohn stated that clearly any formal comparison, other than using the licensed therapeutic range, was misleading in the absence of data from a head-to-head trial in which dose equivalence was properly evaluated.

RESPONSE

Sanofi-Synthélabo stated that there were two versions of Ditropan available. Ditropan IR was an immediate release tablet which had been available for a number of years, and Ditropan XL, a recently launched extended release version. The cost comparison in question was based on the typical daily dose for commonly used medicines for the treatment of urinary incontinence.

Ditropan XL had been proven to have equivalent efficacy to immediate release Ditropan on a mg for mg basis Anderson *et al* (1999), Versi *et al* (2000) and data on file. The summary of product characteristics (SPC) for Ditropan XL stated that 'patients already taking immediate release oxybutynin may be switched to the nearest equivalent total daily dose of Ditropan XL'. Furthermore, experience with Ditropan XL in the USA where it had been available since February 1999, showed that 95% of patients were treated at doses of 10mg daily or less.

A breakdown of the current prescribing of Ditropan in the UK was provided:

Daily dose of oxybutynin (mg)	*% of patients*
Less than 2.5	4.6%
2.5	7.2%
3	1.4%
5	32.0%
6	5.7%
7.5	12.2%
9	1.0%
10	27.3%
15	7.7%
20	1.0%
TOTAL	100%

These data were derived from IMS Medical Data Index (MDI) for Quarter 1 2000 which was the most up-to-date and comprehensive reporting service.

As could be seen from the data, over 91% of patients were treated with doses of 10mg daily or less. Indeed, the most commonly prescribed doses were 5mg and 10mg daily. These were the doses which were shown in the cost comparison chart, whether for Ditropan IR (bd doses) or Ditropan XL (od doses).

Similarly, data derived from the same reporting source (MDI) showed that 65% of patients treated with tolterodine were prescribed doses of 4mg daily or higher, the most common prescription being for 2mg bd. It was for this reason that tolterodine 2mg bd was shown in the cost comparison chart. Furthermore, whilst there had been no direct comparisons between tolterodine and Ditropan XL, there was a study in 378 patients by Malone-Lee (1998) which confirmed equivalent efficacy between tolterodine 2mg bd and Ditropan (IR) 2.5mg bd or 5mg bd (ie the equivalent doses shown for Ditropan XL in this item).

Sanofi-Synthélabo believed that the data shown in the cost comparison chart clearly reflected the most commonly prescribed doses of the medications. The data source was reliable and robust and it denied any breach of the Code.

Turning to the study by Anderson *et al* (1999) quoted by Pharmacia & Upjohn, Sanofi-Synthélabo stated that this was an aggressive dose-titration study to one of three endpoints: the dose at which no incontinence episodes occurred (complete continence), the dose 5mg below that at which anti-cholinergic effects became intolerable, or maximum allowable doses (20mg daily for IR oxybutynin or 30mg daily for Ditropan XL, as per SPC). Therefore, the study pushed patients to higher doses to assess tolerability in addition to efficacy.

The data from this study was shown in the promotional material merely to support the claim of improved tolerability of Ditropan XL compared with Ditropan IR, at the highest licensed doses. It was not shown to support any efficacy claim, nor did it imply typical dose.

Sanofi-Synthélabo concluded that all of the charts in the material were clearly labelled as to their purpose and made no attempt to mislead as to the doses used in the respective studies. Tolerability data was separated from pharmacokinetic data and cost comparison data on different pages. Doses to demonstrate tolerability were deliberately derived from the highest licensed doses, not necessarily as an indicator of typical clinical dosing. Whilst there were no direct comparisons between Ditropan XL and tolterodine, the available data from comparative studies with Ditropan IR; the mg for mg equivalence as noted in the SPC; and the prescribing habits of clinicians clearly supported the comparison of typically used doses shown in the cost comparison chart.

PANEL RULING

The Panel noted that the supplementary information to Clause 7.2 headed 'Price comparisons' stated that 'price comparisons must be accurate, fair and must not mislead. A valid comparison can only be made where like is compared with like'.

The Panel noted that the Detrusitol SPC stated that its recommended dose was 2mg bd. The dose was reduced to 1mg bd in patients with impaired liver function and in the case of troublesome side effects the dose might be reduced to 1mg bd. The Panel noted that according to its SPC the recommended dose for Ditropan XL was 5mg od which might be increased by 5mg a week to achieve a balance of efficacy and tolerability (up to a maximum of 30mg/day). The Panel noted the submission of Sanofi-Synthélabo that 91% of patients were treated with doses of Ditropan of 10mg daily or less. The Panel further noted the statement in the Ditropan XL SPC that those taking immediate release oxybutynin could be switched to the nearest equivalent total daily dose of Ditropan XL.

The Panel noted that Anderson *et al* (1999) compared the efficacy and safety of Ditropan IR and XL for incontinence. The Panel noted Sanofi-Synthélabo's submission that it was an aggressive dose titration study to one of three endpoints and Pharmacia & Upjohn's submission regarding the proportion of patients receiving doses ≥ 15mg daily. There was no direct comparative efficacy evidence for Ditropan XL and Detrusitol. A study by Malone-Lee *et al* 1998 concluded that tolterodine 2mg bd proved equally efficacious to oxybutynin 5mg bd but seemed to be associated with less side effects, particularly dry mouth. There was no claim for equivalent efficacy but the chart might be seen to imply that there was direct evidence of equivalent efficacy. The Panel noted that the most commonly prescribed doses of each medicine had been presented but this had not been made clear. A breach of Clause 7.2 was ruled.

Complaint received **11 August 2000**

Case completed **12 October 2000**

CODE OF PRACTICE REVIEW – NOVEMBER 2000

Cases in which a breach of the Code was ruled are indexed in **bold type**.

986/3/00 & 990/3/00	**General Practitioner and SmithKline Beecham v Lundbeck**	**Antidepressant sampling study**	**Breaches Clauses 2, 4.1, 9.1, 9.8, 9.9, 10.2 and 18.1** **Audit of Lundbeck's procedures required by Appeal Board**	**Appeal by respondent** **Report from Panel to Appeal Board**	**Page 3**
987/3/00	**Consultant Physician v Napp**	**Sponsorship of journal supplement about oxycodone**	**Breaches Clauses 4.1 and 10.1**	**Appeal by complainant**	**Page 10**
988/3/00	**General Practitioner v Novartis**	**Lescol detail aid**	**Breach Clause 3.2 Two breaches Clause 7.2**	**Appeal by respondent**	**Page 13**
993/3/00	**Pharmacist v Bayer**	**Promotion of Lipobay**	**Breach Clause 4.1 Six breaches Clause 7.2**	**Appeal by respondent**	**Page 17**
1008/4/00	**SmithKline Beecham v Aventis Pasteur MSD**	**'Dear Healthcare Professional' letter about Avaxim**	**Two breaches Clause 7.2**	**No appeal**	**Page 30**
1014/4/00	**Consultant Anaesthetist v Elan Pharma**	**Video shown by representative**	**Breaches Clauses 3.2 and 7.2**	**No appeal**	**Page 36**
1016/4/00	Pharmacist v Janssen-Cilag	Presentation on Risperdal	No breach	No appeal	Page 38
1018/4/00	**Insulin Dependent Diabetes Trust v Novo Nordisk**	**Mailing about NovoPen 3**	**Breaches Clauses 20.1 and 20.2**	**Appeal by respondent**	**Page 41**
1024/5/00	**NeXstar/Director v Wyeth**	**Promotion of Abelcet**	**Breaches Clauses 7.2 and 7.6**	**No appeal**	**Page 46**
1025/5/00	General Practitioner v UCB Pharma	Zirtek 'Dear Doctor' letter	No breach	No appeal	Page 48
1026/5/00 & 1027/5/00	**Consultant in Pain Management v Searle and Pfizer**	**Payment to attend meeting**	**No appeal Clause 18.1**	**Page 50**	
1028/6/00	**Director v Schering Health Care**	**Breach of undertaking**	**Breach Clause 21**	**No appeal**	**Page 54**
1030/6/00	Novartis v Fujisawa	Prograf journal advertisement	No breach	Appeal by complainant	Page 56
1031/6/00	**Pharmacist/Director v Schwarz Pharma**	**Breach of undertaking**	**Breaches Clauses 2 and 21**	**No appeal**	**Page 65**
1032/6/00	**Hospital Pharmacist v AstraZeneca**	**Presentation on Accolate**	**Breach Clause 7.2**	**No appeal**	**Page 67**
1033/6/00 & 1039/6/00	General Practitioner v AstraZeneca and Takeda	Amias detail aid	No breach	No appeal	Page 71
1034/6/00 to 1036/6/00	**Clinical Director v Baxter, Bayer and Wyeth**	**Advertisements in Haemophilia**	**Breach Clause 4.1 in each case**	**No appeals**	**Page 73**

1038/6/00	Consultant Ophthalmic Surgeon v Asta Medica	Optilast mailing	No breach	No appeal	Page 76
1040/6/00	**Lilly v Novo Nordisk**	**NovoPen 3 mailing and Helpline**	**Breach Clause 20.1 Two breaches Clause 20.2**	**No appeal**	**Page 77**
1041/6/00	**Consultant Physician v Glaxo Wellcome**	**Payment to attend workshop**	**Breach Clause 18.1**	**No appeal**	**Page 81**
1042/6/00	**Director/Paragraph 16 v Boehringer Ingelheim**	**Teapot and teacup offer**	**Breach Clause 18.1**	**No appeal**	**Page 85**
1044/6/00	**Bristol-Myers Squibb v Aventis Pharma**	**Press releases referring to Taxol and Taxotere**	**Two breaches Clause 7.2 Breach Clause 7.8**	**No appeal**	**Page 86**
1045/7/00	Consultant in Public Health Medicine v Schering-Plough	Supply of Remicade	No breach	No appeal	Page 90
1046/7/00	**Bristol-Myers Squibb and Sanofi-Synthélabo v Solvay Healthcare**	**Teveten journal advertisement**	**Breaches Clauses 7.2 and 7.8**	**No appeal**	**Page 92**
1047/7/00	General Practitioner v Bayer	Lipobay leavepiece	No breach	No appeal	Page 95
1048/7/00	General Practitioner v AstraZeneca	Oxis Turbohaler 12 'Dear Doctor' letter	No breach	No appeal	Page 96
1049/7/00	**Director/Paragraph 16 v Asta Medica**	**Sunglasses offer**	**Breach Clause 18.1**	**No appeal**	**Page 99**
1051/7/00	Consultant Physician v Aventis Pharma	Amaryl leaflet	No breach	No appeal	Page 100
1052/7/00 & 1053/7/00	**Hospital Drug Information Pharmacist v Sanofi-Synthélabo and Bristol-Myers Squibb**	**Plavix promotional card**	**Breach Clause 7.2**	**No appeal**	**Page 102**
1055/7/00 & 1056/7/00	Merck Sharp & Dohme v Procter & Gamble and Aventis Pharma	Actonel journal advertisement	No breach	Appeal by respondents	Page 105
1058/7/00	**General Practitioner v Novartis**	**Stepwise campaign**	**Breach Clause 20.2**	**No appeal**	**Page 109**
1059/8/00	**Anonymous Patient v Wyeth**	**Meeting, wine tasting and social evening**	**Breach Clause 19.1**	**No appeal**	**Page 112**
1060/8/00	**General Practitioner v AstraZeneca**	**Conduct of representative**	**Breaches Clauses 15.2 and 15.3**	**No appeal**	**Page 114**
1064/8/00	**Sanofi-Synthélabo v Lundbeck**	**Sonata detail aid**	**Breach Clause 7.2**	**No appeal**	**Page 116**
1065/8/00	**Pharmacia & Upjohn v Sanofi-Synthélabo**	**Promotion of Ditropan XL**	**Breach Clause 7.2**	**No appeal**	**Page 119**

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, about seventy 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 such medicines made available to the general 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 or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings including payment of travelling and accommodation expenses in connection therewith
- the provision of information to the general public either directly or indirectly
- 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.

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 Nicholas Browne 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 should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 020 7930 9677 facsimile 020 7930 4554).