PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 36 MAY 2002

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.

Remember the non-proprietary name

Companies are reminded that in promotional material, including abbreviated advertisements,the non-proprietary name or list of active ingredients must appear immediately adjacent to the most prominent display of the brand name in bold type of a size such that a lower case 'x' is no less than 2mm in height or in type of such a size that the non-proprietary name or list of active ingredients occupies a total area no less than that taken up by the brand name.

'Immediately adjacent to' means immediately before, immediately after, immediately above or immediately below.

In a 'Dear Doctor' letter, the most prominent display of the brand name will usually be regarded as being the appearance of the brand name in the letter itself rather than that in the prescribing information overleaf, even if the latter is bigger.

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 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 a provider, or potential provider, of services to the industry implies, for example, 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.

Need an audit?

Paragraphs 10.4 and 12.2 of the Constitution and Procedure respectively empower either the Code of Practice Appeal Board or the ABPI Board of Management to require an audit of a company's procedures in relation to the Code to be carried out by the Authority. An audit consists of an examination of a company's procedures for complying with the Code, including certification and such matters as the approval of representatives' expenses, by means of an examination of relevant documents and the questioning of responsible executives. Guidelines on company procedures relating to the Code can be found at pages 40 and 41 in the Code of Practice booklet.

On occasion, the Authority has been asked voluntarily by a company to carry out an audit so that it could be satisfied that its procedures were satisfactory.

If any company wishes to have an audit carried out it is invited to contact the Authority for further information.

Making complaints and responding to them

Inter-company complaints are often accompanied by previous correspondence between the parties. While this is helpful, the provision of such correspondence should not be a substitute for clearly setting out the matters complained of in the actual letter of complaint. The Authority cannot be expected to try to tease out from inter-company correspondence the issues which remain unresolved. Similarly, responses which are accompanied by previous correspondence should deal with all of the matters complained of in the actual letter of response.

When multi-issue complaints are made, it is helpful if the issues are numbered in a logical fashion in the letter of complaint and if the same numbering system is used by the respondent.

The co-operation of companies on these points will assist the Authority in the resolution of complaints.

CODE OF PRACTICE TRAINING

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

These seminars comprise a full day course offering lectures on the Code and the procedures under which complaints are considered, discussion 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:

Friday, 13 September

Monday, 28 October

Wednesday, 27 November

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.

3M HEALTH CARE v NORTON HEALTHCARE

Cactus prescribing service

3M Health Care complained about a document entitled 'Cactus practice effective prescribing', a Norton Healthcare service. This was referred to by Norton Healthcare as the Cactus agreement document. Cactus was a service provided by Baker Norton which enabled general practitioners, primary care groups and health authorities to identify areas within their current prescribing where they could make significant cost savings. No medical or clinical claims were made or implied. Responsibility for prescribing was left firmly with the GP. The motivation behind Cactus was economic, based on balanced comparison of treatment cost using the currently available price data.

3M Health Care stated that in the introductory paragraph of the Cactus agreement document Norton Healthcare claimed that 'many practices in the UK already save thousands of pounds with the help of our computer based system that analyses prescribing'. The claim was not supported by references and 3M Health Care had been unable to receive any supporting material from Norton Healthcare. It therefore considered this claim to be in breach of the Code. 3M Health Care had specifically asked for the methodologies used to calculate the cost savings claimed and had not received these from Norton Healthcare. A further breach of the Code was alleged.

Firstly, the Panel had to decide whether the Cactus system came within the scope of the Code. The system was offered by medical representatives to practices and medical representatives were closely involved. The Cactus system was offered in association with the promotion of Norton's medicines, both by medical representatives and in promotional material. It was therefore subject to the Code. The Panel noted that the claim was not one that required to be referenced. The Panel noted the details and cost savings made during 1999 and 2000 by practices which had carried out prescribing revisions. The Panel considered that the response from Norton Healthcare to 3M Health Care was not unreasonable. A more detailed response to the complaint had been made detailing the calculation methodology. The Panel ruled there was no breach of the Code.

3M Health Care noted that the process included searching for the areas where prescribing could be made more effective, analysing the gathered data, implementation of the actions decided and monitoring of the process on a regular basis. 3M Health Care had serious concerns that non-accredited health professionals would have access to confidential patient data. 3M Health Care believed that such access should be restricted to qualified health professionals. Use of representatives in an inappropriate manner could bring the industry into disrepute.

3M Health Care was also very concerned that changes would be implemented to patients' treatment without appropriate patient participation or consent. 3M Health Care questioned the appropriateness of a non-accredited health professional being allowed to make prescribing changes; such inappropriate use of representatives might breach the Code.

The Panel was concerned that the system support team would have access to confidential patient information. This was denied by Norton Healthcare. The Panel noted that the guidelines on the provision of medical and educational services published in the November 1999 Code of Practice Review stated that only an appropriately qualified person, for example a sponsored registered nurse not employed as a medical/generic representative, might undertake activities relating to patient contact and/or patient identification.

The Panel queried whether each member of the system support team who was not a health professional met the description as being an appropriately qualified person. The Panel noted that the team included nurses and former practice managers. The Panel noted the submission from Norton Healthcare that the searching for patients on repeat prescriptions and revisions was carried out as directed by the GP. The role was to support the GP in implementing practice revisions which were carried out with the GP's approval; at no stage were patients' medical details accessed. The Panel queried how system support teams could carry out revisions without accessing confidential data. Some of Norton Healthcare's comments seemed to imply that access to confidential information by a system support specialist was necessarily acceptable if it had been sanctioned by the GP. Notwithstanding the above reservations, the Panel did not consider that there was any evidence that the system support specialists acted as representatives as defined in the Code and, in consequence, their activities were not subject to the requirements for representatives. In the circumstances, the Panel ruled that there had been no breach of the Code.

3M Health Care noted that Norton Healthcare offered help in 'identifying areas where prescribing could be made more 'practice effective" and 'producing and providing a cost analysis of a practice formulary'. 3M Health Care would be interested to know how Norton would do this. Indeed it would be interested in understanding exactly what 'practice effective' prescribing meant. 3M Health Care had asked Norton Healthcare to provide it with the methodologies used and it had failed to make these available. A breach of the Code was alleged.

The Panel considered that this allegation had some similarities to the first point considered above. The scheme involved switching from branded medicines to branded generics. The Panel considered that the phrases 'practice effective' and 'producing and providing a cost analysis of a practice formulary' were not unacceptable. No breach of the Code was ruled.

3M Health Care Limited complained about a document entitled 'Cactus practice effective

prescribing' (ref CT PSD[BKLT 12.98]), a Norton Healthcare Limited service. This was referred to by Norton Healthcare as the Cactus agreement document.

Norton Healthcare stated that the Cactus service provided by Baker Norton was designed to enable general practitioners, primary care groups and health authorities to identify areas within their current prescribing where they could make significant cost savings. The programme had been in operation for over two years. No medical or clinical claims were made or implied in the process. Prescribing decisions and indeed choice of specific therapy and the responsibility for these decisions were left firmly with the GP. The motivation behind Cactus was essentially an economic argument based on balanced comparison of treatment cost, made using the currently available price data.

Norton Healthcare described the four stages of Cactus.

Stage 1

Once a practice had established that it wished to control its prescribing costs and had discussed this with a Baker Norton healthcare specialist (representative), a system support specialist would carry out an analysis of its current prescribing. This involved a search on various repeat prescriptions. The system support specialists had previously worked within the NHS at practice level and were fully aware of the need for patient confidentiality. In any event, at no stage were patient medical details accessed. At no point was any patient information copied from the computer. This was a confidential search providing top line information for the GPs and authorised practice staff only. This search was carried out only with the prior and documented approval of the practice.

Stage 2

The second stage was to analyse the findings. The number of patients found on each product searched was put into a computer program that provided details of the total amount that the practice could save by switching to less expensive alternatives. Examples of some of the possible recommendations were provided. A Baker Norton representative then presented the findings to the practice staff involved. This would enable the representative to be on hand to answer any questions that might arise from the findings. All the GPs and staff involved decided on the course of action they wished to take. Changes were made only at the request of the GPs.

Stage 3

Once the practice decided it wished to make the savings that had been identified, the system support specialist and Baker Norton representative worked with it to achieve this.

Baker Norton could; revise the repeat prescriptions for the surgery; train a practice employee to revise repeat prescriptions; inform all the administration staff of the changes; inform the local pharmacists of the changes so stocks were available.

Stage 4

Finally, once the practice had completed a change, Baker Norton representatives kept in contact as Norton Healthcare continuously expanded the Cactus service to include further cost effective products. If required, Norton Healthcare provided a second analysis six months later to provide the practice with a report of further potential savings.

At no time was there any breach of patient confidentiality; Norton Healthcare only worked with a practice when it had the full agreement and knowledge of all the partners that worked there, at every stage of the service.

Norton Healthcare provided details of the use of the Cactus agreement document at issue plus other materials. The Cactus agreement document was targeted at GPs and practice managers and distributed by Baker Norton representatives.

Comparisons

All prices were checked monthly, using the current MIMS as a reference document, with updates sent out to representatives, to ensure accuracy. Dosing regimens were as recommended on respective summaries of product characteristics (SPCs), or based on common usage as shown by IMS data on prescribing.

Training Material

In response to requests for further information, Norton Healthcare stated that the service covered a much wider range of therapeutic areas than those in which it had products. Although an internal training document 'What is Cactus?' stated that the service would be able to provide Baker Norton customers with a seamless transition over to CFC-free inhalers, the service was not only concerned with the transition to CFC-free inhalers. The service was sub-contracted to an independent company founded by GPs. Any new products launched by Baker Norton that offered significant cost savings were incorporated into the Cactus programme. Norton Healthcare might also enter into joint promotional arrangements with other companies where cost savings might be available to customers.

Norton Healthcare stated that with regard to repeat prescribing revisions, the switch formulas and the savings evaluation, these related to its own products or products for which it provided data on behalf of the company concerned in marketing the product, such as Wyeth with lanzoprazole.

Other products were covered by the analysis work performed by the subcontracted company; Sections 1-6 and 8-10 of the British National Formulary (BNF) ie all major areas with the exception of bandages and appliances.

The initial analysis could cover any areas that the GP was interested in, although the favoured areas were asthma and gastrointestinal. These areas were often discussed between doctors and representatives as they were areas of typically high spend in general practice. The service covered every medicine area that a GP would be interested in.

Norton Healthcare explained that once the practice had decided to switch, the Baker Norton representative booked the system support specialist to help the practice carry out the revisions, at a mutually convenient time.

The representative also advised the surgery on sending out letters to the patients involved and ensured that all practice staff were aware of the revisions. In addition they would contact local pharmacists to advise them of the changes.

Norton Healthcare stated that the activities of the system support specialists were non-promotional; they were not incentivised by sales results. The role of the system support specialist was to respond to requests for assistance from GP practices that wished to implement computerised revisions to patient medication. These desired revisions might be in response to health authority, PCG or other intervention or might be a result of promotional activity by the Baker Norton sales force.

The system support team did not influence choice of medication for patients but simply helped to implement these changes once requested by the practice. The five team members were all ex-NHS employees, including practice managers and nurses who were familiar with the systems used and indeed recruited on this basis. Importantly, they were all familiar with the protocols involved in handling sensitive information. No patient information was recorded or taken away from the practice in any form.

In summary, the system support team provided an educational and support service to the medical profession.

The training materials included those giving an outline of the process involved. Specific training on systems were given 'on the job' by existing members of the team. Norton did not provide reference documentation for these systems since this was provided to users/purchasers of the systems under copyright, by the original suppliers. However, the company recognised the need to formally document the core processes and protocols for the team and that exercise was now enduring. This would supplement the training given to new starters which included outline of process to be followed including strictly adhering to the sign-off route which ensured that no changes were made without the express request of the GP, confirmed by signature.

The subcontracted company was an independent service specialising in prescribing analyses for health authorities, primary care organisations and individual practices. It did not report to or provide software to Norton Healthcare. Practices sent their PACT data directly to the subcontracted company, Norton Healthcare simply supported the costs of this company running a review for specific practices as educational support to the practice.

Representatives were trained using the actual materials by trainers using a PowerPoint presentation, a copy of which was provided.

1 Cost savings claim

COMPLAINT

3M Health Care stated that in the introductory paragraph of the Cactus agreement document Norton Healthcare claimed that 'many practices in the UK already save thousands of pounds with the help of our computer based system that analyses prescribing'. The claim was not supported by references and 3M Health Care had been unable to receive any supporting material from Norton Healthcare. It therefore considered this claim to be in breach of Clause 7.2 of the Code. 3M Health Care had specifically asked for the methodologies used to calculate the cost savings claimed and had not received these from Norton Healthcare. It considered Norton Healthcare's refusal to provide the substantiation in breach of Clause 7.4 of the Code.

RESPONSE

Norton Healthcare stated that many practices in the UK had saved thousands of pounds as a result of its activities.

In 1999, 360 practices carried out prescribing revisions using Cactus. In the year 2000, 96 practices carried out revisions. The cost savings ranged between £500 and £20,000 for each practice. Three examples were provided. Norton Healthcare therefore did not accept the alleged breaches.

It did note however that the Cactus documentation did not make explicit the sources of product cost data and was happy to undertake to revise future documents to clarify this point.

The methodologies used were outlined in its original reply to 3M Health Care. There was nothing complex about the calculations and, in fact, the comparisons were very straightforward as shown below.

Potential cost savings were calculated by using the difference in cost between puff/dose of original product and equivalent puff/dose of substitute *multiplied by* doses per day of substitute *multiplied by* number of days treatment *multiplied by* number of patients. Two examples were provided.

Again, the allegation that Norton Healthcare had 'refused to give' the methodologies was unfounded. It made it very clear that the methodologies were, in fact, very simple. They could easily have been replicated by 3M Health Care had it desired.

PANEL RULING

The Panel considered that it might have been helpful if it had been provided with more information about the arrangements as a whole. The role of the subcontracted company was unclear. It had however been provided with sufficient information to make rulings on 3M Health Care's allegations. Firstly the Panel had to decide whether the Cactus system came within the scope of the Code. The system was offered by medical representatives to practices and medical representatives were closely involved. The Cactus system was offered in association with the promotion of Norton's medicines, both by medical representatives and in promotional material. It was therefore subject to the Code.

With regard to the specific allegation, the Panel noted that Norton Healthcare had written to 3M Health Care to provide an explanation of the calculation of cost savings. 3M Health Care had written to Norton Healthcare on 9 November and the response from Norton Healthcare was dated 21 December. The Panel queried whether the response was within the Code in relation to the requirement that substantiation be provided without delay. The Panel noted that there was no complaint on this point but considered that its concerns should be drawn to Norton Healthcare's attention.

The Panel noted that the claim was not one that required to be referenced. The Panel noted the details and cost savings made during 1999 and 2000 by practices which had carried out prescribing revisions. The Panel considered that the response from Norton Healthcare to 3M Health Care was not unreasonable. A more detailed response to the complaint had been made detailing the calculation methodology. The Panel ruled there was no breach of Clauses 7.2 and 7.4 as alleged.

2 Use of non-accredited health professionals in effecting prescribing changes

COMPLAINT

3M Health Care stated that Section 3 covered the four stages of the process utilised. These included searching for the areas where prescribing could be made more effective, analysing the gathered data, implementation of the actions decided and monitoring of the process on a regular basis. 3M Health Care had serious concerns that non-accredited health professionals would have access to confidential patient data. 3M Health Care believed that such access should be restricted to qualified health professionals such as nurses and should comply with guidelines from health professional bodies such as the United Kingdom Central Council for Nursing, Midwifery and Health Visiting Code of Professional Conduct. This Code required that registration status was not used in the promotion of commercial products or services. Use of representatives in an inappropriate manner could bring the industry into disrepute.

3M Health Care was also very concerned with the implication in Section 4 that changes would be implemented to patients' treatment without appropriate patient participation or consent. Furthermore, 3M Health Care questioned the appropriateness of a non-accredited health professional being allowed authority to make prescribing changes. 3M Health Care believed that such inappropriate use of representatives might breach Clause 15 of the Code, specifically with reference to Clauses 15.9 and 15.10. These stated that the briefing material provided to medical representatives must comply with the relevant requirements of the Code, and that companies were responsible for the activities of their representatives if these were within the scope of their employment.

RESPONSE

Norton Healthcare stated that whilst Baker Norton representatives were the first point of contact with practices, the actual process of searching, analysing and implementation was facilitated by its small team of system support specialists.

All Baker Norton system support specialists had worked in the National Health Service at practice level, providing them with experience of a variety of computer systems. System support specialists carried out the searching for patients on repeat prescriptions and carried out revisions, as directed by the GP. Their role was to provide support to the GP in implementing practice revisions. If required, practice staff could be trained to carry out revisions. The system support specialists did not carry out a sales function, and were therefore not paid any performance bonuses; based on sales or otherwise. They had no financial incentive to make particular revisions to a practice's prescribing. Thus these people were trained professionals, experienced in the operations of general practice and very familiar with the concepts and requirements of patient confidentiality. Baker Norton was not therefore using 'representatives' in an inappropriate manner. The second part of point 2 referred to changes made to patients' treatment without 'appropriate patient participation'. Norton Healthcare failed to understand why a GP's decision to change a patient's prescription should be challenged by 3M Health Care. The whole point of Cactus was that it was providing a service to GPs that enabled them to maintain control of patients' medication whilst saving money on their drugs budget. So, a patient would be changed from a particular brand of, for example, beclomethasone, to an alternative, less expensive, brand. This gave continuity and was far better for the patient than prescribing generically. Why? Because in the case of generic prescribing the actual medication dispensed was totally uncontrolled by the GP and could be different each time a prescription was dispensed if the pharmacist had bought different products.

Changes made via Cactus or other similar processes gave a positive benefit to the patient and the GP who knew what savings were being made. To argue that changes were made 'without appropriate patient consultation' was ludicrous given that the target for generic prescribing was 72%, ie 72% of all prescriptions so written provided the potential for different alternatives to be supplied at the point of dispensing.

There was no inappropriate use of representatives and therefore no breach of Clause 15 and consequently no breach of Clauses 15.9 and 15.10.

PANEL RULING

The Panel noted that the allegation was that personnel who were not accredited health professionals would have access to confidential patient data and be given authority to make prescribing changes. It was alleged that using representatives in an inappropriate manner could bring the industry into disrepute. The Panel considered that the complaint concerned the status and conduct of the system support specialists. The

Panel did not consider that it had an allegation regarding the role of the sales representatives before it.

The Panel noted the submission from Norton Healthcare that the system support team were familiar with the protocols involved in handling sensitive information.

The Panel was concerned that the system support team would have access to confidential patient information. This was denied by Norton Healthcare. The Panel noted that the guidelines on the provision of medical and educational services published in the November 1999 Code of Practice Review stated that only an appropriately qualified person, for example a sponsored registered nurse not employed as a medical/generic representative, might undertake activities relating to patient contact and/or patient identification.

The Panel queried whether each member of the system support team who was not a health professional met the description as being an appropriately qualified person. The Panel noted that the team included nurses and former practice managers.

The Panel noted the submission from Norton Healthcare that the searching for patients on repeat prescriptions and revisions were carried out as directed by the GP. The role was to provide support to the GP in implementing practice revisions.

The Panel noted the submission that the revisions were carried out with the GP's approval and that at no stage were patients' medical details accessed.

The Panel queried how system support teams could carry out revisions without accessing confidential data. Some of Norton Healthcare's comments seemed to imply that access to confidential information by a system support specialist was necessarily acceptable if it had been sanctioned by the GP.

Notwithstanding the above reservations, the Panel did not consider that there was any evidence that the system support specialists acted as representatives as defined in Clause 1.6 of the Code and in consequence their activities were not subject to the requirements of Clause 15.

In the circumstances, the Panel ruled that there had been no breach of Clause 15.9 of the Code as alleged. Clause 15.10 set out where the responsibility for representatives was placed and could not in itself be breached.

3 Identification of more 'practice effective' prescribing and cost saving calculation

COMPLAINT

3M Health Care stated that Norton Healthcare offered its services in Section 3 of the mailing in '…identifying areas where prescribing could be made more 'practice effective'…'. In Section 6 it offered to provide help in '…producing and providing a cost analysis of a practice formulary'.

3M Health Care would be interested in the methodologies used by Norton in the identification of the areas referred to in Section 3 and in cost-analysing a practice formulary. Indeed it would be interested in understanding exactly what 'practice effective' prescribing meant.

3M Health Care had asked Norton Healthcare to provide it with the methodologies used and it had failed to make these available. 3M Health Care considered this to be in breach of Clause 7.4 of the Code. 3M Health Care would like to ensure that the cost-analysis complied with the guidelines on cost-comparisons of medicines provided by the ABPI and Department of Health.

RESPONSE

Norton Healthcare stated that practice effective prescribing was its term for describing a means for the GP to maintain a chosen therapy for patients whilst minimising the costs associated with the therapy and therefore allowing a given drug budget to be used to treat more patients. The alleged breach was essentially similar to that given under 1 above, costs savings claim, and the same arguments applied in response. In regard to the question as to whether the cost analysis complied with the relevant guidelines, Norton Healthcare confessed a degree of puzzlement as to their relevance to straight price comparisons and they did not provide a basis for complaint.

PANEL RULING

The Panel considered that this allegation had some similarities to that in point 1 above.

The Panel noted that the scheme involved switching from branded medicines to branded generics. The Panel did not consider that the guidelines on the economic evaluation of medicines were relevant in this situation.

The Panel considered that the phrases 'practice effective' and 'producing and providing a cost analysis of a practice formulary' were not unacceptable. No breach of Clause 7.4 of the Code was ruled.

Complaint received **5 March 2001**

Case completed **6 August 2001**

CASE AUTH/1191/6/01

ANONYMOUS GENERAL PRACTITIONER v ORGANON LABORATORIES

Meetings and hospitality

An anonymous general practitioner complained that Organon Laboratories had taken 200 GPs to Moscow for a weekend at a cost of £2000 per head and, in a separate incident, had invited three GPs to dinner at a renowned restaurant with the cost to be £150 per head.

In relation to the Moscow meeting, for which the audience was split 50:50 GPs and consultant gynaecologists, the Panel considered that the actual cost per delegate of £970 plus £70 visa charge was high and would exceed the level that some recipients would normally adopt when paying for themselves. The meeting took place on a Saturday from 9.30am to 4pm, and comprised a number of short scientific presentations. Delegates travelled on Friday afternoon returning on Sunday afternoon; there was an optional tour of Moscow on the Sunday morning. The Panel was concerned that a meeting of mainly UK health professionals was held in Moscow. It considered that the choice of venue was inappropriate and had not been sufficiently justified. The Panel noted the submission that the meeting would have cost a similar amount if it had been held in London. Cost was not the only factor that had to be taken into account. The overall impression was important. The Panel considered that the arrangements for the meeting were unacceptable. A weekend meeting and associated hospitality had been arranged for a scientific programme which lasted less than five hours. There was no cogent or valid reason to hold the meeting in Moscow. The Panel did not consider that the hospitality was secondary to the main purpose of the meeting and therefore ruled a breach of the Code.

In relation to dinner at the restaurant, the Panel noted that it involved three doctors and lasted three hours with about an hour and three quarters spent in discussion. There was no formal agenda. Organon's representative had been asked by one of the doctors to sponsor the meeting with the representatives of two other companies. The doctor had named the venue. When the representative became aware of the potential cost he had tried to withdraw but had been assured by the doctor that the costs would be shared by three representatives and would be kept to a minimum. In the event only the Organon representative and one other had been involved.

No room hire was charged and it therefore appeared that the meeting was held in the public dining room of the restaurant. This was not acceptable for an educational meeting. The total cost of the meal was £85 per head. The Panel did not consider that the arrangements were acceptable. The hospitality was not secondary to the main purpose of the meeting and was out of all proportion to the occasion. The Panel queried whether the cost exceeded the level that the recipients would adopt when paying for themselves. The fact that the cost had been shared with another representative was not relevant. Dividing the cost in this way did not mean that the costs became acceptable as far as the Code was concerned. A breach of the Code was ruled. A further breach was ruled because the Panel did not consider that high standards had been maintained.

As is usual with all cases settled at Panel level, a report was made to the Code of Practice Appeal Board. The Appeal Board was very concerned about the case and decided to report Organon to the ABPI Board of Management. The Appeal Board's view was that Organon should be required to undergo an audit of its procedures. The ABPI Board decided that this was a serious matter. It was accepted that Organon had made errors of judgement which the company had acknowledged and for which contrition had been shown. Organon had demonstrated that this case did not appear to be a result of procedural deficiency. The Board decided that in the circumstances an audit of Organon's procedures would not prove of value and that no further action was necessary, other than expressing its concerns to Organon that such an error of judgement should not be repeated.

An anonymous general practitioner telephoned The Association of British Pharmaceutical Industry (ABPI) to complain about meetings organised by Organon Laboratories Ltd. The telephone message was passed to the Authority and in accordance with established practice it was accepted as a complaint under the Code and dealt with in the usual way.

1 Meeting in Moscow

COMPLAINT

The complainant stated that Organon had taken 200 general practitioners to Moscow for a weekend at a cost of £2,000 per head.

RESPONSE

Organon stated that the meeting held in Moscow was an educational symposium entitled 'Female Healthcare in the Millennium'. The invitation letter made it clear that the objectives of the symposium were to update delegates on current issues and scientific research in the field of women's healthcare and to present some recent data on one of Organon's hormone replacement therapy (HRT) products, Livial.

A total of 158 doctors attended the meeting from all over the UK, plus another 10 from the Republic of Ireland. Overall the audience was split 50:50 between general practitioners and consultant gynaecologists. Delegates were invited by local representatives based on their interest in HRT and the menopause, those involved with osteoporosis strategy development, and those involved in local education of colleagues. Organon stated that it did not allow any partners to attend this event (unless they were also doctors and counted as part of the local region's total number of delegates), and this rule was adhered to strictly. All

delegates had to sign a register on the Saturday morning and were given a certificate of attendance.

All delegates received an invitation, outline programme and reply/acceptance form prior to the event; copies were provided. During the meeting they were provided with a full (final) scientific programme, copies of the abstracts written by each of the speakers, and a meeting evaluation form which they were asked to complete at the end of the scientific session. Copies were provided.

The symposium was presented by an expert speaker panel of eight. The meeting was scheduled to last 4 1/2 hours, but as a result of overruns on some lectures and questions from the floor, the symposium actually finished nearer 4.00pm (not 3.30pm as the original programme).

Organon believed that the scientific content of this meeting was of an excellent standard and overall the lectures were balanced towards issues relevant to female health. Indeed, the proceedings from this meeting would be published as a supplement to the September 2001 edition of the British Menopause Society Journal. Of the scientific content of over 4 hours, only one lecture of half an hour was spent on Livial.

Organon stated that the Royal College of Obstetricians and Gynaecologists (RCOG) advised that it did not award CME points (CPD) in advance of meetings but instead doctors attending the event would decide how much of it to include in their CME diary. Organon needed to submit the register and a summary of the delegate evaluation forms to the RCOG to keep on file. The meeting offered 4 hours of scientific lectures. GPs would use this meeting (or the relevant parts of it) as part of their personal development plans. Based on comments received during the meeting there would be doctors who attended who would use the scientific sessions as part of their continued learning. Organon would also be providing all the delegates with a CD of all the lecture slides presented on the Saturday as a follow-up service.

Delegate feedback following the symposium was positive and the company was currently evaluating the feedback forms for overall appraisal. Other materials available on the day included four clinical papers and a CD-ROM containing principally material on Livial, but also including a comprehensive and educational slide series on HRT and the menopause (osteoporosis, cardiovascular disease, climacteric symptoms etc). Copies of previous Female Healthcare in the Millennium supplements from the British Menopause Society Journal were also available for doctors to take away.

Moscow was chosen for this event based on recommendations from Organon's conference organisers; it was considered that Moscow offered a comparable cost option to any other European city, including London. Delegates were required to travel to Moscow on Friday afternoon to be there in time for a 9.30am Saturday start. The scientific session closed at 4.00pm and was followed in the evening by dinner. As return flights were on the Sunday afternoon, delegates were given the option of a short city tour on Sunday morning before travelling home.

The total cost per delegate was £970, which included two nights' accommodation, flights, all meals, transfers, insurance and travel company support. The only additional charge was £70 per person needed for the travel visa for Moscow. Delegates were asked to provide a deposit cheque of £100 with their acceptance to secure their place.

The costs of running this symposium in London, on the same basis as the Moscow venue, were calculated to be £900 including flight travel costs. Travel costs associated with holding the meeting in London would have included around 70 delegates who would have had to take flights to the meeting. An average travel cost of £127 was calculated. Other delegates would have travelled by rail or by car and furthermore additional unaccounted charges would have been associated with flight transfers, taxis, insurances etc. Therefore the total costs of holding the symposium in London were broadly similar to those in Moscow. The costs mentioned by the complainant were inaccurate.

PANEL RULING

The Panel noted that Clause 19.1 of the Code permitted companies to provide appropriate hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings, scientific congresses and other such meetings. Hospitality must be secondary to the purpose of the meeting and the level of hospitality offered must be appropriate and not out of proportion to the occasion.

The Panel noted that the Code did not prevent companies from holding meetings for UK health professionals at venues outside the UK. There had to be valid and cogent reasons for so doing. When considering whether a meeting and associated hospitality contravened the Code all the circumstances had to be considered including cost, location, educational content, level of hospitality and the overall impression created by the arrangements. Each case had to be considered on its own merits. The programme should attract delegates and not the venue or associated activities.

The Panel considered that the cost of £970 plus £70 visa charge per delegate was high and this would exceed the level that some recipients would normally adopt when paying for themselves.

The Panel examined the documentation provided by Organon. The meeting was entitled 'Female Healthcare in the Millennium Meeting'. It was held in Moscow commencing on the Saturday at 9.30am and finishing at 3.30pm according to the programme. Within that time there were eight, half hour scientific presentations; the meeting started with a 15 minute introduction and ended with a 15 minute panel discussion/summary. The actual meeting overran to 4pm. Delegates were from the UK with a few from the Republic of Ireland. Delegates travelled on Friday afternoon returning on Sunday afternoon. The cost included an optional tour of Moscow on the Sunday morning.

The Panel was concerned that a meeting of UK health professionals (with a few doctors from Eire) was held

in Moscow. It considered that the choice of venue was inappropriate. The Panel noted the submission that the meeting would have cost a similar amount if it had been held in London. Cost was not the only factor that had to be taken into account. The overall impression was important. The Panel considered that the choice of venue had not been sufficiently justified.

The Panel considered that the arrangements for the meeting were unacceptable. A weekend meeting and associated hospitality had been arranged for a scientific programme which lasted less than 5 hours. There was no cogent or valid reason to hold the meeting in Moscow. The Panel did not consider that the hospitality was secondary to the main purpose of the meeting and therefore ruled a breach of Clause 19.1 of the Code. The Panel considered that the educational content, although short, was nonetheless not unreasonable. The Panel did not therefore consider that there had been a breach of Clause 9.1 nor of Clause 2 which was used as a sign of particular censure.

2 GP discussion meeting at a restaurant

COMPLAINT

The complainant further alleged that a representative had invited three GPs to dinner at a renowned restaurant; the cost per head was to be £150.

RESPONSE

Organon stated that the second matter raised by the complainant was similarly inaccurate.

Firstly, the representative named by the complainant was not the representative present at the meeting.

Secondly, it was alleged that costs were in the region of £150 per head. This was incorrect. There were three doctors and two pharmaceutical company representatives present and the half share paid by Organon's representative was £212.25 (ie total costs of £424.50 for 5 persons – £85 per head).

Organon explained that the representative began working on territory fulltime in late March. During his first two weeks on territory he saw a key GP who was involved with PCG matters and had also been involved with educational workshops. The representative enquired about the possibility of discussing PCG issues and the possibility of running a depression workshop. The doctor suggested a meeting with two of his colleagues at the restaurant in question and mentioned that he would also involve two other representatives.

The representative mentioned this meeting to his area sales manager who asked if he was aware of how much it cost at the restaurant and if he knew of its reputation. The representative did not. He had been under the impression that it was a local French or Italian restaurant and had no idea of its reputation. The area sales manager advised the representative to discuss the meeting with his territory partner and as a result a decision was made to withdraw from the meeting, if possible to do so without alienating the customer. The grounds for this were to have been that being new the representative was not aware of budgetary limitations and he was concerned this meeting would extend beyond these. The representative phoned the doctor and said he was unable to justify the cost of the meeting to his manager. The doctor reassured the representative on the grounds that the meeting would be shared by three companies and that the costs would be kept to a minimum.

On the Thursday prior to the meeting the third representative unexpectedly withdrew from the meeting and the representative again expressed his concern and suggested cancellation of the meeting. The doctor reassured the representative that a substitute would be found and the costs would be reasonable.

The meeting lasted from 7.30pm to 10.30pm; approximately one and three quarter hours were spent in discussions. The objectives of the meeting were to: discuss PCG matters, the doctor being a senior member in a group with 11 GPs; evaluate the possibility of the doctor as a potential speaker on the subject of depression; arrange a workshop on managing depression; gain information on an educational group headed by the doctor. As a result of the meeting the above objectives were met and a workshop had been provisionally set up.

The meeting clearly included topics that were not promotional of Organon's products, and the company aimed at promoting the National Service Framework for Mental Health. Indeed the physicians present were contributing expert advice and experience in dealing with mental health issues.

Organon stated that as a result of the complaint it had taken the step of asking the representative to have any future meetings approved by his area sales manager before they were confirmed. This was to ensure that as a new representative, he received the appropriate support to ensure that he developed a clear understanding of meetings allowed within his budget limits and in compliance with the Code.

Organon emphasised that the situation complained of was not simply 'dinner', but a meeting with the objectives described above. The company therefore denied any breach of the Code.

PANEL RULING

The Panel noted the submission that when the representative had seen the doctor he had asked him about the possibility of discussing PCG issues and the possibility of running a depression workshop. The doctor had suggested a meeting with two of his colleagues at the restaurant and had said that he would involve two other representatives. When the representative was made aware of the cost of the restaurant by his manager and territory partner it was decided to withdraw from the meeting without alienating the customer. The doctor reassured the representative it would be reasonable in cost as the meeting would be shared by three companies. One of the two other representatives pulled out.

The Panel noted that the evening meeting lasted three hours with approximately one and three quarter

hours spent in discussion. There was no formal agenda.

The Panel noted that Clause 19 of the Code permitted companies to provide hospitality, stating that 'The level of hospitality offered must be appropriate and not out of proportion to the occasion and the costs involved must not exceed the level which the recipients would normally adopt when paying for themselves'. The Panel also noted the supplementary information to Clause 19 which set out basic principles for any meeting; the meeting must have a clear educational content, the hospitality associated with the meeting must be secondary to the nature of the meeting and must be appropriate and not out of proportion to the occasion. The supplementary information also stated that 'The impression that is created by the arrangements for any meeting must always be kept in mind'. The Panel considered that as a principle, representatives sharing the cost of a meeting would not make otherwise excessive costs acceptable under the Code.

The Panel noted that the meeting took place in a restaurant. No room hire was charged and it therefore appeared that the meeting was held in the public dining room. This was not acceptable for an educational meeting.

The total cost of the meal was £85 per head. The Panel did not consider that the arrangements were acceptable. The hospitality was not secondary to the main purpose of the meeting and was out of all proportion to the occasion. The Panel queried whether the cost exceeded the level that the recipients would adopt when paying for themselves. The fact that the cost had been shared with another representative was not relevant. Dividing the cost in this way, ie two representatives each paying half the cost of the meal, did not mean that the costs became more likely to be acceptable as far as the Code was concerned. The Panel ruled a breach of Clause 19.1 of the Code.

The Panel considered that Organon had failed to maintain a high standard and a breach of Clause 9.1 of the Code was ruled. The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such use. The Panel considered that on balance the circumstances did not warrant such a ruling.

The Panel queried whether Organon had provided sufficient guidance to the representative about organising meetings. The representative was very new and in the Panel's view had had difficult circumstances to deal with. It appeared from the company's submission that although the representative had wanted to discuss certain issues with the doctor it was the doctor himself who had suggested the venue and the involvement of other representatives to spread the cost.

Following its consideration of this case the Panel decided that Organon should be asked to identify the representative who shared the meeting in question.

APPEAL BOARD

As is usual with all cases settled at Panel level, a report was made to the Code of Practice Appeal Board. The Appeal Board was very concerned about the case and decided to report Organon to the ABPI Board of Management. This was in accordance with Paragraph 11.1 of the Constitution and Procedure (1998 Code).

REPORT TO THE ABPI BOARD OF MANAGEMENT

The ABPI Board decided that this was a serious matter. It was accepted that Organon had made errors of judgement which the company had acknowledged and for which contrition had been shown. Organon had demonstrated that procedures were in place and this case did not appear to be a result of procedural deficiency. The Board decided that in the circumstances an audit of Organon's procedures would not prove of value and that no further action was necessary, other than expressing its concerns to Organon that such an error of judgement should not be repeated.

Complaint received	**11 June 2001**
Case completed	**19 July 2001**
PMCPA proceedings completed	**13 December 2001**
ABPI Board proceedings completed	**12 February 2002**

CASE AUTH/1222/8/01

GLAXOSMITHKLINE v PFIZER

Relpax Clinical Summary

GlaxoSmithKline complained about data included in the Relpax (eletriptan HBr) Clinical Summary produced by Pfizer. GlaxoSmithKline marketed Imigran (sumatriptan).

The claim 'Consistently demonstrated superior relief of migraine headache compared with sumatriptan', and associated figures, were supported by data from two published head-to-head studies (Goadsby *et al* 2001 and Pryse-Phillips *et al* 1999) and a meta-analysis of three comparative studies (Hettiarachchi 2000). The primary efficacy endpoint was the percentage of patients with headache relief 2 hours after treatment. Encapsulated sumatriptan was used to blind each of the studies; eletriptan was not encapsulated. It was stated that encapsulated sumatriptan was bioequivalent to the marketed (non-encapsulated) formulation. The study used to support bioequivalence was conducted by Pfizer (Milton *et al* 2001) and demonstrated in healthy volunteers that encapsulation of sumatriptan tablets did not alter the area under the plasma concentration-time curve from 0 to infinity (AUC_∞). GlaxoSmithKline noted, however, that the study did not focus on the effects of encapsulation during the time period referred to in the clinical summary (2 hours) and nor did it look at the effects in migraine patients themselves. Plasma drug concentrations during the first 2 hours after dosing were critical in determining the 2 hour response to sumatriptan – the key end-point used in the eletriptan comparative studies.

From Milton *et al* GlaxoSmithKline estimated the sumatriptan plasma concentrations during the first 2 hours after dosing and showed that the estimated data for the encapsulated formulation did not match those for the non-encapsulated, marketed formulation. At 30 minutes, the time at which sumatriptan started to work, the plasma concentration of sumatriptan was over 60% less after encapsulated sumatriptan than after non-encapsulated sumatriptan. These data were in line with another study (Fuseau *et al* 2001) in which the early absorption of the encapsulated formulation (defined as AUC_2) was shown to be reduced by 21% in healthy volunteers and reduced by 27% in patients who were experiencing a migraine attack. The latter result was to be expected as gastric stasis, which occurred during a migraine attack, could slow drug absorption. An alternative formulation that had pharmacokinetic parameters within the 80-125% range of the standard formulation was usually referred to as bioequivalent. In healthy volunteers the lower AUC_2 for the encapsulated formulation compared with the non-encapsulated formulation fell outside this range (reduced by 21%) and this was even more marked in migraine patients (reduced by 27%). All three of the head-to-head studies used to infer greater efficacy of eletriptan compared with sumatriptan were conducted with encapsulated sumatriptan tablets. In addition, in a study sponsored by Merck Sharp & Dohme (Visser *et al* 1996), both rizatriptan and sumatriptan were over-encapsulated. The range of response rates (using the standard definition of headache relief at 2 hours) from all the studies using encapsulated sumatriptan (46% - 55%) were lower than those in all other comparator studies where sumatriptan was not encapsulated (57% - 68%).

In Visser *et al*, the over-encapsulation lowered the efficacy of both products (rizatriptan 52%, sumatriptan 46%). Subsequent Merck Sharp & Dohme studies used non-encapsulated sumatriptan tablets and produced correspondingly increased response rates (rizatriptan 62 - 72%, sumatriptan 62 - 68%). GlaxoSmithKline provided a bar chart comparing response rates at 2 hours for encapsulated and non-encapsulated sumatriptan 50mg and 100mg across all the published comparator studies and stated that this illustrated that the delayed absorption in migraine patients during the first 2 hours after dosing with encapsulated sumatriptan was translated into reduced efficacy at 2 hours. Given the bias inherent in the design of the three comparative trials, GlaxoSmithKline believed that these trials could not be considered adequate and well controlled clinical trials capable of supporting the comparison and the claim for superior efficacy.

The Panel noted that the booklet presented data from three different clinical studies and a pooled analysis comparing the efficacy, in terms of headache response at 2 hours post-dose, of sumatriptan and Relpax. Where the lowest recommended dose of sumatriptan (50mg) had been studied, one study and the pooled analyses, 50 and 53% of patients reported a headache response at 2 hours respectively; with the higher dose (100mg), three studies and the pooled analysis, responses reported were 55%, 55%, 53% and 54% of patients respectively. Relpax 40mg produced a response in 65%, 65%, 64% and 64% of patients with 77%, 77%, 67% and 71% of patients responding to an 80mg dose. In all of the studies the efficacy of the highest dose of Relpax (80mg) was statistically significantly greater than that of the highest dose of sumatriptan (100mg).

The sumatriptan used in the studies was the standard commercially available 100mg tablet enclosed, without backfill, in a gelatin capsule. Milton *et al* reported that the encapsulated sumatriptan was bioequivalent to the commercially available product. The AUC_∞ values were 201.95 and 199.74ng h/ml for the standard and the encapsulated sumatriptan respectively. The maximum observed plasma concentrations (C_{max}) values were 58.91 and 56.09ng/ml respectively (the Imigran summary of product characteristics (SPC) stated that after a 100mg dose, the maximum plasma concentration was 54ng/ml). Milton *et al* reported that the time to maximum concentration (T_{max}) was 1.69 and 1.83 hours respectively and stated that both forms of sumatriptan were thus bioequivalent using the standard range of 80-125%. The T_{max} data suggested a similar rate of absorption. The authors concluded that even if borderline differences in bioequivalence did sometimes occur, it was highly

unlikely to be clinically relevant because studies had failed to find consistent dose response effects for sumatriptan. In this regard the Panel noted that the Imigran SPC stated that doses of 25-100mg had shown greater efficacy than placebo in clinical trials, but 25mg was statistically significantly less effective than 50 and 100mg. A review of the clinical pharmacokinetics of sumatriptan stated that there was no evidence of a correlation between plasma concentration of sumatriptan and its therapeutic effect in relieving migraine headache (Scott 1994).

GlaxoSmithKline had cited Fuseau *et al* which demonstrated that in both healthy volunteers and migraine patients encapsulated sumatriptan 50mg delayed the absorption of the medicine in the time from 0 to 2 hours post-dose (AUC_2 reduced by 21% and AUC_2 reduced by 27% respectively). This delay in absorption compared to the conventional tablet might account for the lower efficacy of sumatriptan in some comparative studies. The Panel noted, however, that in this study the 50mg sumatriptan tablet was enclosed in a gelatin capsule filled with 0.5% magnesium stearate in lactose; this was not the same form of encapsulation as used by Milton *et al*. With regard to the difference in absorption seen in healthy volunteers compared to that in patients with migraine, the Panel noted that the Imigran SPC stated that the pharmacokinetics of oral sumatriptan did not appear to be significantly affected by migraine attacks. With regard to the typical response rate to sumatriptan 100mg, the Panel noted that Tfelt-Hansen (1998) reported that overall in twelve placebo-controlled double-blind randomized clinical trials the percentage of patients responding at 2 hours was 58% with a 25% response rate seen with placebo and a therapeutic gain of 33%. Tfelt-Hanson (2000) reported that overall in twenty placebo-controlled double-blind randomized clinical trials the percentage of patients responding at 2 hours was 59% with a 28% response rate seen with placebo and a mean therapeutic gain of 32%. The Panel noted that in the comparative studies of Relpax and sumatriptan the number of patients responding at 2 hours to 100mg sumatriptan was 53-55% with therapeutic gains of 22-31%. In the Panel's view this response rate was not inconsistent with that reported by Tfelt-Hansen.

Overall the Panel considered that there was data to show that the Pfizer-encapsulated sumatriptan was bioequivalent to the commercially available tablets and that such encapsulation did not reduce the efficacy of sumatriptan with regard to headache relief at 2 hours. The response rates shown with the encapsulated sumatriptan were not inconsistent with those shown with the non-encapsulated form. The Panel did not consider that the data presented was misleading as alleged and no breach of the Code was ruled.

Upon appeal by GlaxoSmithKline, the Appeal Board noted that the claim'Consistently demonstrated superior relief of migraine headache compared with sumatriptan' related to headache response at 2 hours postdose. The head-to-head trials from which the data were taken had involved the use of encapsulated sumatriptan. The basis of the complaint was that the encapsulation of the sumatriptan resulted in a lower than expected response to the medicine. Milton *et al*, which had been used to demonstrate the bioequivalence of the encapsulated sumatriptan with the marketed (non-encapsulated) formulation, had calculated AUC_∞ as one of its primary measures. The Appeal Board noted the Pfizer representatives' submission at the hearing that the study was not powered to detect differences in the pharmacokinetics of the two forms of sumatriptan between 0 and 2 hours and Pfizer's view that the maximum observed plasma concentrations, C_{max}, for the encapsulated and non-encapsulated Imigran were equivalent. It also noted the extensive pharmacokinetic data supplied by Pfizer. GlaxoSmithKline's limited post hoc analysis of the Milton *et al* data estimated that between 0 and 2 hours there was a 16-21% decrease in the AUC for encapsulated sumatriptan compared to the non-encapsulated formulation, thus suggesting that encapsulation of sumatriptan reduced its absorption in the first 2 hours post-dose. Such a reduction in the AUC_{0-2}, while not proven by GlaxoSmithKline, was equally not excluded by Pfizer's response.

The Appeal Board noted that in migraine therapy it was the acute response to a medicine which was important; this was reflected in the efficacy studies in which headache response at 2 hours postdose was the prime efficacy criterion. The Appeal Board noted that there was no corresponding pharmacokinetic data provided by Pfizer to prove that encapsulated sumatriptan was bioequivalent to the marketed product over this time period. The Appeal Board considered that it had not been sufficiently demonstrated that encapsulated sumatriptan would not affect response to treatment over 0 to 2 hours. In that regard the Appeal Board considered that the claim was misleading and a breach of the Code was ruled.

GlaxoSmithKline stated that by the side of each of the figures in the clinical summary comparing Relpax with sumatriptan there was a statement that all patients who received Relpax experienced significantly greater relief compared with placebo. As there was no such statement for sumatriptan, the implication was that the difference between sumatriptan and placebo did not reach statistical significance. GlaxoSmithKline believed that not including the significance value for sumatriptan, or at least a statement to the effect that this was not analysed in the study, was misleading. The Panel noted that the page heading was 'Consistently demonstrated superior relief of migraine headache compared with sumatriptan'. In this context the Panel considered that a positive statement about Relpax would imply the opposite was true for sumatriptan. Although the clinical trials had not statistically analysed the difference in response between placebo and sumatriptan, the Panel considered that the statement about Relpax gave a misleading impression about the efficacy of sumatriptan as alleged and the bar charts were thus misleading in this regard. A breach of the Code was ruled. This ruling was not appealed.

GlaxoSmithKline stated that on the front page of the clinical summary there was a statement to the effect that full prescribing information could be found

inside the pocket. However, the inside pocket contained the Relpax SPC. The Panel noted that prescribing information must form part of promotional material and must not be separate from it. The booklet contained, in a pocket on the inside back page, a loose copy of the SPC. The Panel noted that the prescribing information was not the same as the SPC. The prescribing information required a succinct statement of the information in the SPC relating to the certain aspects of prescribing and should also contain details of cost; a matter not included at all in an SPC. The Panel considered that the prescribing information for Relpax had not been provided and a breach of the Code was ruled. This ruling was not appealed.

GlaxoSmithKline complained about data included in the 'Relpax (eletriptan HBr) Clinical Summary', a 16 page booklet produced by Pfizer Limited which had been distributed, including to those present from the UK, at the World Congress of Neurology held at London in June 2001. GlaxoSmithKline marketed Imigran (sumatriptan).

1 Claim 'Consistently demonstrated superior relief of migraine headache compared with sumatriptan'

COMPLAINT

GlaxoSmithKline noted that this claim, and the figures on pages 3-5 of the clinical summary, were supported by data from two published head-to-head studies against sumatriptan (Goadsby *et al* 2001 and Pryse-Phillips *et al* 1999) and a meta-analysis of three comparative studies (Hettiarachchi 2000), all conducted by Pfizer. The primary efficacy endpoint was the percentage of patients with headache relief 2 hours after treatment.

In each of the studies, encapsulated sumatriptan was used to blind the study; eletriptan was not encapsulated. It was stated in the clinical summary that encapsulated sumatriptan was bioequivalent to the marketed (non-encapsulated) formulation. The study used to support bioequivalence was conducted by Pfizer and published by Milton *et al* (2001).

GlaxoSmithKline's key areas of concern were:

a) The bioequivalence study conducted by Pfizer and two subsequent studies conducted by GlaxoSmithKline demonstrated that encapsulation delayed the absorption of sumatriptan over the first 2 hours after dosing. The encapsulated sumatriptan was therefore not bioequivalent to the marketed formulation over the time period for which the data was presented (the first 2 hours).

b) A comparison of response rates with encapsulated and non-encapsulated sumatriptan indicated that this delayed absorption translated into reduced response rates at 2 hours.

a) Encapsulation delayed the absorption of sumatriptan in healthy volunteers, and this effect was enhanced in migraine patients.

The bioequivalence study conducted by Pfizer in healthy volunteers (Milton *et al*) demonstrated that encapsulation of sumatriptan tablets did not alter the area under the plasma concentration-time curve from 0 to infinity (AUC_∞). However, the report of this study did not focus on the effects of encapsulation during the time period referred to in the clinical summary (2 hours) and nor did it look at the effects in migraine patients themselves. Plasma drug concentrations during the first 2 hours after dosing were critical in determining the two hour response to sumatriptan – the key end-point used in the eletriptan comparative studies.

Using data from Milton *et al* it was possible to estimate the sumatriptan plasma concentrations during the first 2 hours after dosing with the two formulations. These data were illustrated in a graph provided by GlaxoSmithKline which stated that they showed that the plasma concentrations for the encapsulated formulation did not match those for the non-encapsulated, marketed formulation. At 30 minutes, the time at which sumatriptan started to work, the plasma concentration of sumatriptan was over 60% less after encapsulated sumatriptan than after non-encapsulated sumatriptan. These data were in line with another study (Fuseau *et al* 2001) which found that early absorption of the encapsulated formulation (defined as AUC_2) was reduced by 21% in healthy volunteers. In patients who were experiencing a migraine attack early absorption was reduced by 27% during the 2 hours after dosing. This was to be expected as gastric stasis, which occurred during a migraine attack, could slow drug absorption.

An alternative formulation that had pharmacokinetic parameters within the 80-125% range of the standard formulation was usually referred to as bioequivalent. In healthy volunteers the lower AUC_2 for the encapsulated formulation compared with the non-encapsulated formulation fell outside this range (reduced by 21%) and this was even more marked in migraine patients (reduced by 27%).

b) Response rates to encapsulated sumatriptan at 2 hours were lower than those seen in all other comparator studies.

All three of the head-to-head studies used to infer greater efficacy of eletriptan compared with sumatriptan were conducted with encapsulated sumatriptan tablets. In addition, in a study sponsored by Merck Sharp & Dohme (Visser *et al* 1996) both rizatriptan and sumatriptan were over-encapsulated in order to avoid bias.

The range of response rates (using the standard definition of headache relief at 2 hours) from all the studies using encapsulated sumatriptan (46% - 55%) were lower than those in all other comparator studies where sumatriptan was not encapsulated (57% - 68%).

In Visser *et al* (1996), the over-encapsulation lowered the efficacy of both products (rizatriptan 52%, sumatriptan 46%). Subsequent Merck Sharp & Dohme studies used non-encapsulated sumatriptan tablets and produced correspondingly increased response rates (rizatriptan 62 - 72%, sumatriptan 62 - 68%).

GlaxoSmithKline provided a bar chart comparing response rates at two hours for encapsulated and non-

encapsulated sumatriptan 50mg and 100mg across all the published comparator studies. GlaxoSmithKline stated that this illustrated that the delayed absorption in migraine patients during the first 2 hours after dosing with encapsulated sumatriptan was translated into reduced efficacy at 2 hours.

Given the bias inherent in the design of the three comparative trials, GlaxoSmithKline believed that these trials could not be considered adequate and well controlled clinical trials capable of supporting a drug-to-drug comparison and a claim for superior efficacy. As such, GlaxoSmithKline alleged a breach of Clause 7.2.

GlaxoSmithKline commented further on the Pfizer encapsulation data.

Sumatriptan plasma concentrations A table was provided showing the percentage difference in sumatriptan plasma concentrations between encapsulated and marketed (non-encapsulated) formulations. The data was estimated from Milton *et al*.

Sumatriptan dose-response at 2 hours Pfizer, in a written response to GlaxoSmithKline's primary concerns, had stated that there was no dose-response relationship for oral sumatriptan. Although not stated, GlaxoSmithKline took this to imply that Pfizer considered any difference in the 'dose' provided by the encapsulated and non-encapsulated formulations to be of no clinical relevance. This was flawed on two accounts:

- Although a large sumatriptan dose-ranging study did not reveal any statistically significant difference between the 50mg and 100mg doses after 2 hours, subsequent studies had shown that some patients did respond more favourably to the 100mg dose.
- Two-hour dose-response studies using only non-encapsulated sumatriptan did not provide any relevant information for direct comparison with responses to encapsulated formulations over this time period when the rate of absorption was critically reduced. The lack of validity in any attempted comparison was further highlighted by the fact that encapsulation reduced early absorption.

Markers of bioequivalence Pfizer, in a written response to GlaxoSmithKline's concerns, had pointed out that the use of AUC_{∞} and C_{max} for bioequivalence were regulatory standards. This was not disputed. However, they might not be the most direct efficacy markers for the triptans, or indeed any drug that required a rapid onset of action. For triptans, the response was primarily evaluated between 0 and 2 hours. Consequently, partial AUCs such as AUC_2 (0-2hrs) were more relevant. The FDA had acknowledged the use of such partial AUCs in its recent guidance for industry on bioavailability and bioequivalence studies.

Therapeutic gain and NNT GlaxoSmithKline stated that in order to compare the efficacy of migraine treatments across studies, several authors had conducted meta-analyses to determine the therapeutic gain (drug response rate at 2 hours – placebo response rate) and NNT (numbers needed to treat) values for the triptans.

The range of therapeutic gain values for sumatriptan 50mg and 100mg across these analyses was 30 - 35%. The therapeutic gain for encapsulated sumatriptan from the Pfizer studies was 23% (from the pooled analysis across all three comparative studies). These data further illustrated that encapsulation reduced the 2 hour response rate for sumatriptan. The range of NNT values for sumatriptan (50-100mg) was 2.9 - 3.1. However, the NNT value for encapsulated sumatriptan (from the pooled analysis of the Pfizer studies) was 4.3 - 4.5 which was outside the 95% confidence intervals from the meta-analyses.

GlaxoSmithKline provided a table showing therapeutic gain and NNT for various formulations of sumatriptan.

RESPONSE

Pfizer believed GlaxoSmithKline's complaint to be without scientific merit and that there had been no breach of Clause 7.2.

In the comparative trials supporting the claim 'Consistently demonstrated superior relief of migraine headache compared with sumatriptan', Pfizer employed encapsulation to blind the sumatriptan comparator. Encapsulation of a comparator to maintain blinding in a clinical study was a common and accepted practice; in fact, GlaxoSmithKline used this method to blind a comparator drug in one of its own trials. In blinding the sumatriptan comparator by encapsulation, Pfizer acted in good faith and proceeded according to accepted scientific and regulatory principles and standards by providing *in vitro* dissolution data and conducting standard bioequivalence testing to validate the blinding method.

Pfizer commented on the three main elements of GlaxoSmithKline's complaint.

GlaxoSmithKline's concern that encapsulated sumatriptan used in the Pfizer studies was not bioequivalent to the marketed tablet formulation.

Encapsulated sumatriptan used in the Pfizer comparator studies was bioequivalent to the marketed formulation based on all standard bioequivalence and dissolution criteria. Pfizer conducted an *in vivo* bioequivalence study in which the encapsulated formulation of sumatriptan used in eletriptan clinical trials was found to meet well-established bioequivalence criteria, endorsed by both EMEA and FDA. Dissolution testing showed that *in vitro* dissolution rates were comparable for commercial sumatriptan tablets vs the encapsulated formulation of sumatriptan used in the Pfizer comparator studies. Both formulations showed 100% dissolution within 15 minutes. Pfizer provided a supporting graph and referred to Milton *et al*.

The bioequivalence studies that GlaxoSmithKline conducted were not relevant to the results of the Pfizer comparator studies. GlaxoSmithKline used an encapsulation method substantially different from the method used in the Pfizer-sponsored comparator

studies. Among the variables involved were the composition of the capsule, the contents of the capsule, the method of backfill compaction and the manufacturing specifications.

The encapsulated formulation of sumatriptan used by Pfizer in its comparator trials resulted in plasma concentrations of sumatriptan that were bioequivalent to the commercial tablet as well as being well within the range of plasma concentrations that had been reported for the same dose (100mg) in previously published pharmacokinetics studies.

Pfizer provided a figure showing the median C_{max} (maximal concentration) and range achieved by the Pfizer encapsulated formulation compared to the three doses of the commercial formulation. Pfizer stated that this demonstrated that the plasma concentrations for the Pfizer-encapsulated sumatriptan fell well within the range of concentrations obtained for the 100mg sumatriptan dose in GlaxoSmithKline's own pharmacokinetics studies, further supporting equivalence of the encapsulated sumatriptan with the commercial tablet.

GlaxoSmithKline's concern that although Pfizer-encapsulated sumatriptan was bioequivalent by standard criteria, early (0-2 hour) bioequivalence criteria should be applied instead because they were more clinically relevant.

In relation to GlaxoSmithKline's concerns that '... use of [standard] AUC and C_{max} for bioequivalence ... may not be the most direct efficacy markers for the triptans, or indeed any drug that requires a rapid onset of action ... partial AUCs such as AUC_2 (0-2 hrs) are more relevant', Pfizer stated that existing data did not support use of non-standard (0-2 hours) bioequivalence for sumatriptan. Pfizer noted that GlaxoSmithKline cited a US FDA Guidance (not referenced in the EMEA guidance) to support its call for early pharmacokinetics and bioequivalence criteria. The FDA Guidance made it clear that 'early exposure measures may be indicated on the basis of appropriate clinical efficacy or safety trials and/or pharmacokinetic/pharmacodynamic studies'. In this case, such non-standard (0-2 hour) bioequivalence criteria were not justified because there was no clinical evidence of a significant correlation between the dose of oral sumatriptan (or the plasma levels reached between 0 and 2 hours) and headache response at 2 hours.

Clinical data consistently showed that oral sumatriptan had a flat dose-response curve, and that the efficacy of sumatriptan was not correlated with dose or plasma concentrations. This lack of dose-response was reflected in the United States Package Insert (USPI) and the UK summary of product characteristics (SPC) for sumatriptan. The USPI label for sumatriptan stated 'There were no statistically significant differences between the 50- and 100-mg groups in any study' and 'There is evidence that doses above 50mg do not provide a greater effect than 50mg'. Section 5.1 of the SPC for sumatriptan noted that the 100mg and 50mg doses were only statistically significant compared to the 25mg dose (not compared to each other).

Pfizer provided a bar chart which it stated showed the 2 hour headache response rates from the three pivotal studies that GlaxoSmithKline submitted to the FDA in support of its original New Drug Application (NDA) for oral sumatriptan. There was no dose-response relationship, despite the fact that treatment with the 25mg and the 50mg doses both resulted in proportionately lower plasma levels at all time points up to 2 hours.

GlaxoSmithKline, in multiple previously published pharmacokinetic and bioequivalence studies of sumatriptan, had never utilised the early (0-2 hour) bioequivalence criteria that it now proposed as more clinically relevant. GlaxoSmithKline did not use these early bioequivalence criteria when it established the bioequivalence of the film-coated (ie marketed) sumatriptan tablet compared to the dispersible tablet used in its development program. Even GlaxoSmithKline's recent study, Fuseau *et al*, was not designed or powered to evaluate these early bioequivalence criteria.

Pfizer noted that GlaxoSmithKline had cited data from three studies to demonstrate that there was a dose-response curve for oral sumatriptan. However, none of the three studies were designed as dose-response studies, and none provided scientifically credible evidence that sumatriptan had a dose-response.

Salonen *et al* (1999) was an open-label crossover study whose 'primary endpoints were patient dose preference'. The study was not designed to evaluate the standard International Headache Society (IHS) efficacy endpoint, headache response, or the comparative efficacy of different doses, although open-label efficacy data was presented as a secondary endpoint. Even with open label efficacy data, it should be noted that there was no statistically significant difference in headache response at 30 minutes, 1 hour, or 2 hours for the 50mg vs the 100mg dose, or for the 25mg dose vs the 50mg dose.

Dowson *et al* (1999) was not a double-blind, parallel-group placebo-controlled study. Instead, it was a 'patient selected dosing' study that provided no evidence of the differential efficacy of 25mg vs 50mg vs 100mg of oral sumatriptan. As such, it contained no controlled data regarding the efficacy of sumatriptan.

Cady *et al* (2000) reported results from the Spectrum study. This phase of the Spectrum study was designed to evaluate the differential efficacy of early vs late treatment intervention. The standard IHS baseline criteria for headache response (presence of moderate to severe headache prior to treating) were not used. Further a dose-response comparison of 50mg vs 100mg was not the primary outcome.

GlaxoSmithKline's concern that the lack of bioequivalence, and the delayed absorption caused by encapsulation, translated into reduced response rates at 2 hours for the encapsulated formulation of sumatriptan compared to the tablet formulation.

Pfizer stated that the headache response rates for Pfizer-encapsulated sumatriptan (based on therapeutic gain) were consistent with those for sumatriptan used in clinical trials cited in published literature and with those included in the USPI. The

therapeutic equivalence of the sumatriptan used in the Pfizer studies was further supported by a comprehensive meta-analysis based on all published well-controlled sumatriptan studies. This analysis demonstrated that the efficacy of Pfizer-encapsulated sumatriptan, at both 1 hour and 2 hours, was comparable to results obtained in studies using the commercial formulation.

GlaxoSmithKline's conclusion, that Pfizer-encapsulated sumatriptan had a reduced headache response at 2 hours, was incorrect and based on its selective review and misleading presentation of the data. In fact, the efficacy of Pfizer-encapsulated sumatriptan showed no reduction in headache response, but was fully comparable to the efficacy of the commercial sumatriptan tablet. This conclusion was based on a comprehensive review of headache response rates for the 100mg sumatriptan tablet obtained from sixteen published placebo-controlled sumatriptan studies and was further supported by the results of a meta-analysis.

GlaxoSmithKline had supported its claim that headache response was reduced for the encapsulated formulation of sumatriptan, compared to the tablet formulation, by reporting two different types of data.

GlaxoSmithKline presented a figure that purported to show that encapsulated sumatriptan had a lower 2 hour headache response than commercial sumatriptan tablets. The figure was flawed for the following reasons.

- The figure represented a selective review of the available data. It omitted many of the placebo-controlled studies included in the two meta-analyses presented below. Similarly, it did not include several of the triptan comparator studies summarized in the Tfelt-Hansen (2000) review article.
- The figure mixed eight placebo-controlled studies with three non-placebo-controlled studies. This was inappropriate because patients enrolled in placebo-controlled studies responded differently to patients enrolled in non-placebo-controlled studies. Due to the expectation of receiving active agent, patients in such studies tended to have higher response rates.
- The figure included studies whose placebo response varied by more than 20%, but without performing scientifically required corrections for differences in placebo response rates. In three of the studies the placebo response rate was above 40% yet still no correction was made.
- When correction was made for placebo response rate differences (ie therapeutic gain was calculated), the study shown in the figure having the highest therapeutic gain for the 100mg dosage form was achieved by the Pfizer-encapsulated formulation of sumatriptan.
- GlaxoSmithKline combined in one figure headache response data for both the 50mg and the 100mg doses of the tablet formulation of sumatriptan. This was inconsistent and misleading in light of its claim that sumatriptan had a dose-response curve. In fact, the two highest headache response rates shown in the figure were for the 50mg doses of sumatriptan.

For the reasons cited above, the figure provided by GlaxoSmithKline was misleading and did not provide strong scientific evidence to support the claim that the tablet formulation of sumatriptan had higher efficacy than the encapsulated formulation.

A scientifically more appropriate version of this figure (as provided by Pfizer) would, per IHS guidelines, include only placebo-controlled studies, and would compare the therapeutic gain on a dose-by-dose basis. The efficacy of the Pfizer-encapsulated formulation of sumatriptan could be seen to be therapeutically equivalent to that of the tablet formulation, once the widely varying non-specific placebo effect was appropriately factored out.

Pfizer noted that GlaxoSmithKline had cited data from several references to support its claim that the 'therapeutic gain' from the encapsulated formulation of sumatriptan was reduced compared to the tablet formulation. It concluded 'These data further illustrate that encapsulation reduces the 2 hour response rate for sumatriptan'.

Although it was correct to report data in terms of therapeutic gain, there were problems with the references cited by GlaxoSmithKline to support its conclusion that Pfizer-encapsulated sumatriptan had a lower response rate. Specifically, the majority of the references cited did not report the results of an actual meta-analysis using appropriate methodology. Instead the references cited were review articles that summarized some, but not all, of published data on the efficacy of oral sumatriptan tablets: each of the references cited by GlaxoSmithKline omitted one or more of the studies cited in the meta-analysis that Pfizer provided in a summary.

Rather than the selective review of existing data presented by GlaxoSmithKline, a Medline search (1980-2001) revealed sixteen double-blind, placebo-controlled trials employing 100mg sumatriptan tablets. When correction was made for varying response rates in these individual studies (ie data were presented as therapeutic gain), the response rates for the encapsulated sumatriptan used in the Pfizer studies were well within the range of headache responses reported in these sixteen studies.

The meta-analysis, being prepared for peer-reviewed publication, showed that the headache response rate was the same for Pfizer-encapsulated vs tablet forms of sumatriptan at both 2 hours and at 1 hour. The results of this meta analysis were summarized in figures provided by Pfizer, one of which compared the therapeutic gain for headache response at 2 hours for Pfizer-encapsulated sumatriptan vs tablet sumatriptan from sixteen published studies. Pfizer stated that the results for both formulations showed therapeutic responses in the same range.

Another figure showed the therapeutic gain for headache response at 1 hour for Pfizer-encapsulated sumatriptan vs tablet sumatriptan from six published studies. Once again, the results for both formulations showed therapeutic responses in the same range. The comparable efficacy of Pfizer-encapsulated

sumatriptan at 1 hour was significant in that it was contrary to GlaxoSmithKline's assertion that encapsulation resulted in reduced efficacy at early time points. Another showed the effect size calculation for both the 1 hour and 2 hour headache response data. The effect sizes for Pfizer-encapsulated sumatriptan were very similar to the tablet formulation at both time points.

An independent meta-analysis (Roon *et al* 2001) reported results that were consistent with the results shown in the previous three figures. The results of this meta-analysis supported the conclusion that encapsulation did not reduce efficacy at early time points. The therapeutic gain at one hour for sumatriptan 100mg was 15%, similar to the one hour results for Pfizer-encapsulated sumatriptan.

It should be noted that the meta-analysis showed a therapeutic gain of 20% at one hour for the 80mg dose of eletriptan – significantly higher than the therapeutic gain reported for the 100mg dose of sumatriptan. The 95% confidence intervals around the therapeutic gain for each medicine were not found to be overlapping. This latter result provided independent confirmation of data from the Pfizer sumatriptan comparator studies, which also found superiority of the 80mg dose of eletriptan compared to the 100mg dose of sumatriptan.

GlaxoSmithKline had briefly cited data on NNT. It should be noted that NNT was simply a different method of calculating and presenting the results discussed in the previous points. Therefore the same criticisms that were highlighted above regarding therapeutic gain also applied to the NNT data presented by GlaxoSmithKline.

Pfizer concluded that the evidence presented by GlaxoSmithKline to support its claim that Pfizer-encapsulated sumatriptan had a reduced headache response at 2 hours compared to the tablet formulation of sumatriptan relied on selective reporting of data. In a meta-analysis and/or systematic review of the efficacy of triptans in the acute treatment of migraine, it was of paramount importance to report data on all appropriate placebo-controlled trials. GlaxoSmithKline's evidence did not meet this requirement.

Evidence based on both individual studies and a meta-analysis of placebo-controlled studies (Roon *et al* 2001) clearly demonstrated that Pfizer-encapsulated sumatriptan showed a therapeutic effect that was fully comparable, both at one hour and at two hours, to what had been reported for the tablet form of sumatriptan.

In the previous sections Pfizer had demonstrated in detail that the two Pfizer-sponsored comparator studies using encapsulated sumatriptan were scientifically valid and fair comparisons. The claim of superiority, therefore, was established and the GlaxoSmithKline complaint was without scientific merit.

The superiority results of Pfizer's fair comparisons of eletriptan vs sumatriptan had been cross-validated by two independent comparative analyses of triptan efficacy. Firstly the paper by Roon *et al*, as stated above, and secondly in the review by Tfelt-Hansen *et al* (2000) which was the most comprehensive ever published comparing the headache response data across all marketed triptans. The results were summarized in the abstract of the paper and illustrated in a figure. These results showed that among oral triptans, eletriptan had the highest therapeutic gain.

The results of these two independent evaluations of the comparative efficacy of triptans provided strong cross-validation of the results of the two Pfizer-sponsored direct comparator trials.

Summary

Pfizer stated that the encapsulated sumatriptan used in its comparator studies met all regulatory criteria for bioequivalence. Furthermore, there were no available data showing a significant relationship between early pharmacokinetics parameters and headache response at 2 hours that justified the use of the early bioequivalence criteria proposed by GlaxoSmithKline.

Contrary to GlaxoSmithKline's complaint, the encapsulated sumatriptan used in the Pfizer studies demonstrated efficacy, in terms of headache response at both one hour and two hours, that was comparable to commercially available sumatriptan tablets. This clinical equivalence was confirmed by the results of sixteen published studies and a meta-analysis of published data.

Regarding GlaxoSmithKline's final complaint, that the Pfizer comparator studies 'were not ... capable of supporting a drug-to-drug comparison, and a claim of superior efficacy', Pfizer had demonstrated not only that its study was valid, but had cited two independent analyses (Tfelt-Hansen *et al*, 2000; Ferrari *et al*, 2001) which both reported similar superiority results for eletriptan that cross-validated the findings of the Pfizer study.

Based on the evidence summarized above, the information, claims and comparisons presented by Pfizer in the Relpax clinical summary were accurate, fair and based on strong scientific evidence which was clearly reflected in the content. Based upon a view of all available clinical data, the evidence suggested that the Pfizer comparator studies were adequate and well-controlled clinical trials supporting a drug-drug comparison and a claim of superior efficacy. The clinical summary could not, in Pfizer's view, be said to mislead either directly or by implication. GlaxoSmithKline's complaint, therefore, was based on selective reporting of existing data, and was without sufficient scientific merit. Pfizer's position was that it had not breached of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that pages 3-5 of the Relpax Clinical Summary booklet presented data from three different clinical studies and a pooled analysis comparing the efficacy, in terms of headache response at 2 hours post-dose, of sumatriptan and Relpax. Where the lowest recommended dose of sumatriptan (50mg) had been studied, one study and the pooled analyses, 50 and 53% of patients reported a headache response at 2

hours respectively; with the higher dose (100mg), three studies and the pooled analysis, responses reported were 55%, 55%, 53% and 54% of patients respectively. Relpax 40mg produced a response in 65%, 65%, 64% and 64% of patients with 77%, 77%, 67% and 71% of patients responding to an 80mg dose. In all of the studies the efficacy of the highest dose of Relpax (80mg) was statistically significantly greater than that of the highest dose of sumatriptan (100mg).

The Panel noted that the sumatriptan used in the studies was the standard commercially available 100mg tablet enclosed, without backfill, in a gelatin capsule. Milton *et al* reported that the encapsulated sumatriptan was bioequivalent to the commercially available product. The area under the plasma concentration-time curve from 0 to infinity (AUC) values were 201.95 and 199.74ng h/ml for the standard and the encapsulated sumatriptan respectively. The maximum observed plasma concentrations (C_{max}) values were 58.91 and 56.09ng/ml respectively (section 5.2 of the lmigran SPC stated that after a 100mg dose, the maximum plasma concentration was 54ng/ml). Milton *et al* reported that the time to maximum concentration (T_{max}) was 1.69 and 1.83 hours respectively and stated that both forms of sumatriptan were thus bioequivalent using the standard range of 80-125%. The T_{max} data suggested a similar rate of absorption. In their conclusions the authors noted that even if borderline differences in bioequivalence did sometimes occur, it was highly unlikely to be clinically relevant because studies had failed to find consistent dose response effects for sumatriptan. In this regard the Panel noted that section 5.1 of the Imigran SPC stated that doses of 25-100mg had shown greater efficacy than placebo in clinical trials, but 25mg was statistically significantly less effective than 50 and 100mg. In a review of the clinical pharmacokinetics of sumatriptan Scott (1994) stated that there was no evidence of a correlation between plasma concentration of sumatriptan and its therapeutic effect in relieving migraine headache.

The Panel noted that GlaxoSmithKline had cited the results of Fuseau *et al* which demonstrated that in both healthy volunteers and migraine patients an encapsulated form of sumatriptan 50mg delayed the absorption of the medicine in the time from dosing to 2 hours after dosing. This delay in absorption compared to the conventional tablet, which was greater in the migraineurs (AUC_2 reduced by 27%) than in the volunteers (AUC_2 reduced by 21%), might account for the lower efficacy of sumatriptan in some comparative studies. The Panel noted, however, that in this study the 50mg sumatriptan tablet was enclosed in a gelatin capsule filled with 0.5% magnesium stearate in lactose. The encapsulated form of sumatriptan studied by Fuseau *et al* was thus not the same as that studied by Milton *et al*. With regard to the difference in absorption seen in healthy volunteers compared to that in patients with migraine, the Panel noted that the Imigran SPC stated that the pharmacokinetics of oral sumatriptan did not appear to be significantly affected by migraine attacks.

With regard to the typical response rate to sumatriptan 100mg, the Panel noted that the review by Tfelt-Hansen (1998) reported that overall in twelve placebo-controlled double-blind randomized clinical trials the percentage of patients responding at 2 hours was 58% with a 25% response rate seen with placebo and a therapeutic gain of 33%. Tfelt-Hanson (2000) reported that overall in twenty placebo-controlled double-blind randomized clinical trials the percentage of patients responding at 2 hours was 59% with a 28% response rate seen with placebo and a mean therapeutic gain of 32%. The Panel noted that in the comparative studies of Relpax and sumatriptan the number of patients responding at 2 hours to 100mg sumatriptan was 53-55% with therapeutic gains of 22-31%. In the Panel's view this response rate was not inconsistent to that reported by Tfelt-Hansen.

Overall the Panel considered that there was data to show that the Pfizer-encapsulated sumatriptan was bioequivalent to the commercially available tablets and that such encapsulation did not reduce the efficacy of sumatriptan with regard to headache relief at 2 hours. The response rates shown with the encapsulated sumatriptan were not inconsistent with those shown with the non-encapsulated form. The Panel did not consider that the data presented was misleading as alleged and no breach of Clause 7.2 was ruled.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline stated that the claim and the figures on pages 3-5 of the clinical summary were supported by data from two published head-to-head studies against sumatriptan, and a meta-analysis of three comparative studies, all conducted by Pfizer. The primary efficacy endpoint was the percentage of patients with headache relief two hours after treatment. GlaxoSmithKline believed that there was bias inherent in the design of these studies, and therefore that they could not be considered adequate and well-controlled clinical trials capable of supporting a drug-to-drug comparison, and a claim for superior efficacy. As such, the company considered their use to be a breach of Clause 7.2 of the Code.

In each of the studies, encapsulated sumatriptan was used to blind the study, whereas eletriptan, the Pfizer compound, was not encapsulated.

The key areas of concern addressed in the original complaint were:

a) The bioequivalence study conducted by Pfizer, and two subsequent studies conducted by GlaxoSmithKline, demonstrated that encapsulation delayed the absorption of sumatriptan over the first two hours following dosing. The encapsulated sumatriptan was therefore not bioequivalent to the marketed formulation over the time period for which the data was presented (the first two hours).

b) A comparison of response rates obtained with encapsulated and non-encapsulated sumatriptan indicated that this delayed absorption translated into markedly reduced response rates at two hours.

Pfizer's defence of its comparative studies (subsequently upheld by the Panel) involved three main points: the method of encapsulation used in

GlaxoSmithKline-sponsored pharmacokinetic studies was different to that used in the Pfizer-sponsored comparative clinical studies; Imigran did not have a dose-response relationship and was therefore insensitive to small differences in plasma concentrations within the first two hours after dosing; the therapeutic gain for encapsulated Imigran 100mg indicated that it was within the range of therapeutic gains for non-encapsulated Imigran 100mg.

Before dealing with each of these three points GlaxoSmithKline considered it important to note that Pfizer's defence was entirely based on data for the 100mg dose of Imigran. However, the recommended dose of Imigran in the UK was 50mg. When the data for the recommended dose was also examined, Pfizer's arguments were unsustainable. Furthermore although Pfizer's response went into detailed pharmacokinetic arguments the true issue at the heart of this case was: Was there a marked and consistent difference in efficacy when Imigran was encapsulated, compared with when it was not encapsulated? If the answer to this was yes, then data obtained with encapsulated Imigran versus non-encapsulated comparator were inherently misleading, and the precise reasons as to the cause of this were secondary.

Method of encapsulation

Pfizer's argument was that the method of encapsulation in GlaxoSmithKline-sponsored pharmacokinetic studies was different to that used in the Pfizer-sponsored comparative clinical studies.

GlaxoSmithKline reiterated its belief that the $AUC_{0-\infty}$ was not an appropriate method of assessing the bioequivalence of encapsulated vs non-encapsulated migraine treatments. Milton *et al* demonstrated that in healthy volunteers encapsulation of sumatriptan tablets did not alter the area under the plasma concentration-time curve from 0 to infinity ($AUC_{0-\infty}$). Although this parameter was a regulatory standard, GlaxoSmithKline contended that it was not the most direct efficacy marker for the triptans, or indeed any drug that required a rapid onset of action. The prime efficacy criterion assessed in acute migraine trials was headache relief at two hours (or earlier), as stated by the International Headache Society in its Guidelines for Controlled Trials in Migraine. Consequently, partial AUCs such as AUC_{0-2} were more relevant. The FDA and MCA had acknowledged the use of such partial AUCs in their guidance on bioavailability and bioequivalence studies.

The Panel, in its ruling, accepted Pfizer's representation that the two encapsulation methods were different; and therefore that the GlaxoSmithKline data were not applicable. However, the Panel might not have appreciated that the reduction of absorption over the first two hours with encapsulated Imigran occurred with both methods of encapsulation. Milton *et al*, incorporating the encapsulation method used in the Pfizer comparative studies, indicated a 16-21% reduction in absorption of sumatriptan for the encapsulated formulation compared with the marketed formulation during the first two hours. This was in line with the 21% reduction seen in the GlaxoSmithKline pharmacokinetic study in healthy volunteers (27% in migraine patients). These data suggested that the reduction in absorption was not dependent on the encapsulation methodology, contrary to Pfizer's assertion. GlaxoSmithKline provided a bar chart giving data from Fuseau *et al* and Milton *et al*.

Dose response

Pfizer's argument was that Imigran did not have a dose response relationship and therefore was insensitive to small differences in plasma concentrations in the first two hours after dosing.

GlaxoSmithKline reiterated that Pfizer had carefully concentrated its defence solely on the 100mg dose of Imigran, a fact that might not have been fully appreciated by the Panel when reaching its decision. However, there was a clear and acknowledged dose-response relationship for the tablet formulation of Imigran: Imigran 25mg was significantly less effective than both Imigran 50mg and Imigran 100mg. As noted above, 50mg, was the recommended dose of Imigran; and, as such, the dose-response differential between the 50mg and 25mg doses might be highly relevant in assessing the efficacy evidence presented below.

Efficacy

GlaxoSmithKline stated that the acid test of whether encapsulated Imigran was equivalent to non-encapsulated Imigran was in their relative efficacy. If there was a consistent difference in the efficacy between the two formulations, then this in itself indicated that the comparison between the formulations was inherently flawed. GlaxoSmithKline contended that the data obtained by Pfizer with encapsulated Imigran showed consistently inferior response rates to those seen with the overwhelming majority of other studies, and hence did not reflect the balance of evidence. Pfizer's argument was that the therapeutic gain for encapsulated Imigran 100mg indicated that it was within the range of therapeutic gains for non-encapsulated Imigran 100mg.

GlaxoSmithKline's response was that the relative efficacy of encapsulated versus non-encapsulated Imigran could only be accurately assessed in a comparative study. As no such comparison existed, in order to determine whether encapsulation did indeed lower the efficacy of Imigran, it was necessary to compare across studies and assess the balance of evidence.

Pfizer maintained that the therapeutic gain (active response rate at two hours minus the placebo rate) for Imigran 100mg was within the range seen with non-encapsulated Imigran 100mg. However, with any medicine, a range of responses was seen across studies. The fact that some studies with medicine A indicated an efficacy within the range of that seen with studies of medicine B, did not in itself indicate that both medicines had equivalent efficacy. GlaxoSmithKline provided an illustrative figure. Furthermore, the therapeutic gain for encapsulated Imigran 50mg (as opposed to 100mg) seen in the

Pfizer studies was only 16-19%, well outside that seen with non-encapsulated Imigran 50mg.

Therapeutic gain: the balance of the evidence

The main thrust of the Pfizer defence that encapsulated Imigran was equivalent to non-encapsulated Imigran was based on its own meta-analysis. This analysis was highly selective (it only included data for 100mg) and contained errors. Specifically:

1 Pfizer had included twice a study comparing zolmitriptan with Imigran 100mg. This study had been heavily criticised, as it incorporated a randomisation ratio of 1:8:8 (placebo: Imigran 100mg: zolmitriptan 5mg). This severely imbalanced randomisation resulted in very high placebo rates and so the study was unable to show significant efficacy for either active arm over placebo. This was clearly contrary to all other published triptan studies, and GlaxoSmithKline therefore believed that it was inappropriate to include it in an analysis where placebo response rate was subtracted from that of the active treatment. It should certainly not be included twice.

2 Pfizer had also included (again twice) a study comparing Imigran 100mg with placebo (Centonze *et al* 1995 and Nappi *et al* 1994), in which the therapeutic gain (20%) was the lowest of the range seen with Imigran 100mg.

3 Pfizer included only the interim results of the early Imigran dose-defining study.

Comparing the 'results' obtained by Pfizer with the therapeutic gains seen in independent analyses clearly indicated that encapsulation reduced the efficacy of Imigran in the first two hours. GlaxoSmithKline provided a supporting bar chart.

GlaxoSmithKline stated that the consistency of the therapeutic gain for the non-encapsulated formulations of Imigran in independent meta-analyses was striking. However, Pfizer discounted many of these analyses on the basis that they did not include all of the data – although clearly the completeness of the individual data sets was largely dependent on the date of publication – and because of a 'lack of appropriate methodology'. Although GlaxoSmithKline did not agree with this rationale, the most recently published independent meta-analysis in The Lancet was presumably acceptable, and therefore particularly informative (Ferrari *et al* 2001). The authors showed that the therapeutic gain for non-encapsulated Imigran 50mg was 32% (estimated from the figure) and 29% for Imigran 100mg (95% CI, 26-34%). These data were clearly in line with previously published meta-analyses. Whilst GlaxoSmithKline did not necessarily agree with all the conclusions stated by Ferrari *et al* the authors did make some important points:

- 'The sumatriptan efficacy rates were very consistent across companies except for low pain free and sustained pain free rates in the comparator studies versus eletriptan.'
- 'In the direct comparator trials versus eletriptan, sumatriptan (but not eletriptan) was encapsulated (for masking purposes) and significantly underperformed for freedom from pain compared with other trials.'
- 'The great strength of randomised head-to-head comparator trials is their internal validity. However, factors such as patient selection, study size and encapsulation of a drug may limit the generalisibility of the results into clinical practice.'

Furthermore, this analysis did not support an improved efficacy for the recommended dose of eletriptan (40mg) over the recommended dose of Imigran (50mg), or Imigran 100mg. This directly contradicted the results of the studies shown in the eletriptan clinical summary. The data did suggest that twice the recommended dose of eletriptan (80mg) might have increased efficacy (and side-effects) compared with Imigran 50 and 100mg.

Therapeutic gain for non-encapsulated and encapsulated formulations in published comparator studies

As supportive evidence, GlaxoSmithKline reproduced again the response rates seen with Imigran across all of the comparator studies. These were particularly relevant as they represented data from comparator studies similar to those sponsored by Pfizer.

The range of response rates (using the standard definition of headache relief at two hours) from all of the comparator studies using non-encapsulated Imigran (59%-68%) were higher than those in all comparator studies in which Imigran was encapsulated (46%-57%). A bar chart was provided by GlaxoSmithKline.

Of particular relevance, Visser *et al* (1996) sponsored by Merck Sharp & Dohme used encapsulated Imigran 100mg. In this scientifically robust study, both rizatriptan and Imigran were over-encapsulated. The over-encapsulation lowered the efficacy of both triptans (rizatriptan 52%, sumatriptan 46%). Subsequent Merck Sharp & Dohme studies used non-encapsulated Imigran tablets and produced correspondingly increased response rates (rizatriptan 62-72%, Imigran 62-68%).

Summary and conclusions

GlaxoSmithKline stated that taken together, these data clearly indicated that encapsulation consistently reduced the early absorption of Imigran, and that this was translated into an equally consistent and clinically significant reduction in the efficacy of Imigran over the first two hours after dosing. GlaxoSmithKline therefore believed that results of a comparative study of encapsulated Imigran vs non-encapsulated eletriptan should not be used to claim superiority of eletriptan 40mg over Imigran 50mg or 100mg. The use of this study to claim such a superiority was misleading and did not reflect the balance of the available data. GlaxoSmithKline therefore maintained that the item in question was in breach of Clause 7.2 of the Code.

COMMENTS FROM PFIZER

Pfizer considered GlaxoSmithKline's appeal was

without merit. Its response sought to demonstrate that Pfizer-encapsulated Imigran was bioequivalent and clinically equivalent to the non-encapsulated formulation. Pfizer summarised its original response to the complaint and then addressed GlaxoSmithKline's appeal.

Pfizer stated that it would address each point made by GlaxoSmithKline in its appeal but would focus primarily on the one key issue that GlaxoSmithKline itself had identified as the 'heart' of the matter.

'… the true issue at the heart of this case was: Was there a marked and consistent difference in efficacy when Imigran was encapsulated, compared with when it was not encapsulated? If the answer to this was yes, then data obtained with encapsulated Imigran versus non-encapsulated comparator were inherently misleading, and the precise reasons as to the cause of this were secondary.'

Pfizer accepted the clinical efficacy premise laid out by GlaxoSmithKline in the paragraph above. Pfizer maintained that its superiority claim was valid because: (1) encapsulation did not result in a 'consistent and marked difference in efficacy' for Imigran when efficacy data was compared for encapsulated vs non-encapsulated Imigran, and (2) the superior efficacy of Relpax vs Imigran (documented by the head-to-head comparator trials reported in the Clinical Summary) had been definitively confirmed by Ferrari *et al*, the comprehensive meta-analysis of triptan efficacy cited by GlaxoSmithKline in its appeal. This independent confirmation of the superior efficacy of Relpax convincingly established that the results from the Pfizer-sponsored comparator trials were not an anomaly, but were consistent with the weight of available data worldwide.

Though emphasizing the primary importance of clinical efficacy, nonetheless GlaxoSmithKline, in its appeal, revisited technical issues regarding encapsulation, bioequivalence, and pharmacokinetics.

GlaxoSmithKline submitted that 'there was a clear and acknowledged dose-response relationship for the tablet formulation of Imigran'

Pfizer stated that whether encapsulation might have any clinical relevance depended completely upon whether Imigran had a significant dose-response relationship. If doubling the dose (and the plasma level) of Imigran made no difference in terms of efficacy, then any argument about minor fluctuations in plasma level at various time-points was not clinically relevant.

Contrary to the claim of GlaxoSmithKline, Imigran showed no dose-response effect for 50mg vs 100mg, and only a minimal dose-response effect for 25mg vs both 100mg and 50mg. Extensive clinical trials data had established that headache response to Imigran was independent of whether the dose used was 50mg or 100mg. Pfizer reiterated that the lack of a dose-response difference in efficacy was cited in both the USPI labelling, and the UK SPC labelling for oral Imigran. The recent Ferrari *et al* meta-analysis also made this clear; a figure from which showed that there was no meaningful difference in efficacy between the 2 doses. An examination of the figure suggested that even a 4-fold dose increase – from 25mg up to 100mg – yielded only a modest dose-response effect, which amounted to approximately a 7% higher response rate. It was important to note that the only evidence presented in GlaxoSmithKline's appeal in favour of even a weak dose-response effect came from citing data on a 25mg dose which was not licensed in the UK.

GlaxoSmithKline was concerned about the clinical significance of a lack of a dose-response effect for 50mg vs 100mg of Imigran

Pfizer stated that if Imigran 50mg worked as well as 100mg, then this meant that the 50mg dose resulted in a plasma level that was already sufficient to achieve the maximal therapeutic response. In other words, the plasma concentration-response curve had reached a plateau ie the plasma level above which there was no further gain in efficacy despite further increases in either dose or plasma concentration (E_{max}). For medicines such as the triptans where therapeutic effect was mediated by activity at key receptors, the E_{max} reflected the plasma concentration that provided a sufficient amount of drug to saturate the available receptors. For oral Imigran, the E_{max} occurred somewhere between the 25mg and 50mg dose. As GlaxoSmithKline's own studies had shown, additional dose increases were associated with no additional increase in efficacy, whether the dose was raised to 100mg, or as high as 200mg or 300mg.

The efficacy of Imigran might vary from patient to patient, and from study to study, but these differences could not be attributed to fluctuations in plasma level (whether due to encapsulation, or some other reason), once E_{max} had been reached. This view was confirmed by Visser *et al* who looked at non-responders to subcutaneous Imigran to evaluate whether lower plasma levels might account for non-response. The authors concluded that 'lack of headache relief after sumatriptan does not appear to be explained by pharmacokinetic or pharmacodynamic differences between patients'. Patient response to Imigran (and all triptans) might vary due to many other clinical variables that had nothing to do with pharmacokinetics, or with plasma levels (or with encapsulation).

As noted above, somewhere between the dose of 25mg and 50mg, the dose-response curve for Imigran reached its plateau. Based on extensive efficacy and pharmacokinetic data, one might estimate the E_{max} plasma level for oral Imigran. The result was illustrated in a figure provided by Pfizer and was near the median C_{max} for Imigran 50mg. The figure also showed the results from GlaxoSmithKline-sponsored pharmacokinetic studies of oral Imigran and the results from pharmacokinetic studies of Pfizer-encapsulated 50mg and 100mg of Imigran. The figure showed that the 50mg dose of Imigran, whether it was encapsulated or not still yielded a C_{max} that was at or above the E_{max}.

One additional point about the figure was to note that despite the high variability in C_{max} after oral Imigran, the vast majority of patients appeared to have achieved plasma concentrations that were at, or above, the plasma concentration-response E_{max} for

Imigran. The figure also illustrated the extent to which oral Imigran administration resulted in wide variability in plasma levels.

GlaxoSmithKline's concerns about encapsulation and bioequivalence

Pfizer noted that GlaxoSmithKline had reiterated that although the AUC and C_{max} criteria as required by the FDA/EMEA was a regulatory standard, it contended that partial AUC (in the first 2 hours) was 'more relevant'. Pfizer reiterated its objection to the post-hoc imposition of a bioequivalence criterion that was not the regulatory standard and was never previously applied by GlaxoSmithKline in its published bioequivalence and pharmacokinetic studies. GlaxoSmithKline had defended its proposals for a new bioequivalence criterion, stating: 'partial AUCs such as AUC_{0-2} are more relevant. The FDA and MCA have acknowledged the use of such partial AUCs in their guidance on bioavailability and bioequivalence studies'.

GlaxoSmithKline provided in its appeal, without additional comment, two highlighted sections of the FDA and EMEA Guidelines on Bioequivalence/ Bioavailability. Pfizer noted that it had cited these guidelines in its original response, but it wished to reiterate now the point that it made previously: it was certainly true that partial AUCs might be relevant for some medicines, but only if these early (ie, 'partial') AUC values were 'justified' (EMEA Guidance) 'on the basis of appropriate clinical efficacy/safety trials and/or pharmacokinetic/pharmacodynamic studies' (FDA Guidance). As Pfizer previously had noted, GlaxoSmithKline had conducted no such studies on oral Imigran, and had presented no data to show that there was a relationship between the clinical efficacy of oral Imigran, and early pharmacokinetic parameters such as early AUC_{0-2}. This was clearly what both guidances required, that new bioequivalence criteria be justified 'on the basis of appropriate' studies and data. This standard had not been met by GlaxoSmithKline, nor had it held itself to this standard in its own bioequivalence studies.

Using this unjustified post-hoc standard, GlaxoSmithKline included a visually effective graph in its appeal which showed an apparent 21% reduction in the area under the curve ('AUC') at the particular post-hoc time point chosen by GlaxoSmithKline. In addition to disputing this criterion, Pfizer would like to place this 21% 'reduction' in context and noted that despite the '21% reduction', the C_{max} of encapsulated Imigran 100mg was still equivalent to the C_{max} of non-encapsulated Imigran 100mg. The same could be said for encapsulated vs non-encapsulated 50mg doses of Imigran; and both were above the Imigran plasma E_{max}.

One might conclude that even if GlaxoSmithKline's new bioequivalence criteria were used, the 21% reduction at the 2 hour time point was still clinically irrelevant for 2 reasons. Firstly, the 21% 'reduction' was minimal given the greater than 100% variability in plasma concentrations reported for the same dose of non-encapsulated Imigran. In fact, because of this high plasma level variability, this 'reduction' was not statistically significant, but instead was just random fluctuation around a small sample size mean. Secondly the 'reduced' plasma C_{max} achieved at 2 hours by encapsulated Imigran was still clearly above the E_{max} for the medicine – ie, the plasma level beyond which no additional efficacy was observed.

GlaxoSmithKline's concern that Pfizer 'carefully concentrated its defence solely on the 100mg dose of Imigran'

Pfizer stated that it elected to compare the 100mg dose of encapsulated vs non-encapsulated Imigran for several reasons. First, the highest available therapeutic dose generally provided a more stringent test of efficacy superiority than use of a lower dose as a comparator. Had Pfizer not compared Relpax to Imigran 100mg, then GlaxoSmithKline (in keeping with its belief that there was a dose-response effect) might have complained about an unfair comparison to the lower 50mg dose. In fact, it appeared somewhat paradoxical for GlaxoSmithKline to argue that it was 'carefully concentrating' its discussion of headache response on Imigran 100mg. Either oral Imigran did not have a dose-response curve (in which case the 100mg dose was certainly an equivalent, and more conservative, proxy for the 50mg dose), or it did have a dose-response curve, in which case the 100mg dose was the more stringent test of efficacy. To cover both alternatives, Pfizer opted for emphasizing the 100mg comparison.

There was, however, a second scientific reason for basing an encapsulated vs non-encapsulated comparison on Imigran 100mg instead of 50mg. As GlaxoSmithKline itself had noted, one of the ways of validating the results of the Pfizer head-to-head comparator studies was to compare them with results from other studies of oral Imigran which GlaxoSmithKline rightly referred to as 'the balance of the evidence'. To examine the balance of the evidence, one relied on meta-analysis, and the reliability of a meta-analysis increased in direct proportion to the number of available studies (the quality of the studies and their design were also important). There were three times as many studies available on the 100mg dose compared to the 50mg dose of Imigran. For this additional scientific reason Pfizer chose the more reliable 100mg dose. Use of a dose in which multiple studies were available was especially important given the highly variable therapeutic gain exhibited by Imigran in clinical trials. This sort of variability 'averaged out' when a larger number of studies were available.

In claiming that the 50mg dose was the more appropriate comparison, GlaxoSmithKline stated that in the UK '50mg is the recommended dose'. Pfizer considered this to be misleading. In fact, 50mg was the recommended starting dose. At the time of initial approval, 100mg was the approved dose of Imigran in Europe. Later data showing similar efficacy for 50mg but better tolerability resulted in the change to a recommendation that 50mg be the starting dose for all patients. This further underlined the lack of a clear efficacy dose response between 50mg and 100mg Imigran. It was important to note that the IMS

prescription database showed that last year 36% of patients on oral Imigran were taking the 50mg dose, while 64% were taking the 100mg dose. For this additional reason it seemed appropriate for a comparison of encapsulated vs non-encapsulated Imigran to focus on the 100mg dose.

GlaxoSmithKline claimed that 'the acid test of whether encapsulated Imigran was equivalent to non-encapsulated Imigran was their relative efficacy', and that Pfizer's encapsulated Imigran had not met this test

Pfizer noted that in its original response it had addressed this clinical equivalence issue based on the results of its own meta-analysis of published literature, corroborated by two other systematic and comparative reviews. However, Ferrari *et al* provided an even more comprehensive meta-analysis that included results from unpublished clinical trials (therefore eliminating any possible 'publication bias'). The results of Ferrari *et al* provided two types of corroboration of the head-to-head study results presented in the Clinical Summary:

1. The results demonstrated that the efficacy of encapsulated Imigran was in the same range reported by Ferrari *et al*. The mean therapeutic gain for encapsulated Imigran from the Clinical Summary was 26.5%. The mean therapeutic gain for Imigran from the meta-analysis of all studies was 29%

2. The results of Ferrari *et al* also provided independent confirmation of the headache response superiority of Relpax compared to Imigran. This was clear from inspection of the figure referred to above which showed a separation of means, with minimal to no overlap of 95% confidence intervals, for both the 40mg and 80mg dose of Relpax vs Imigran 100mg (the relative lack of available studies made the confidence intervals much wider and the meta-analysis much less reliable for the 50mg dose of Imigran). The superior 2 hour headache response of Relpax vs Imigran was one of the conclusions of Ferrari *et al*.

Ferrari *et al* presented powerful evidence that clearly demonstrated the clinical equivalence of encapsulated vs non-encapsulated Imigran. In its appeal GlaxoSmithKline stated 'We contend that the data obtained by Pfizer with encapsulated Imigran show consistently inferior response rates to those seen with the overwhelming majority of other studies, and hence do not reflect the balance of the evidence'. Pfizer's response to this was that Ferrari *et al* contained all of the available published and unpublished sumatriptan efficacy data, and the results for the two Pfizer-encapsulated studies was right in the mid-range of all of the studies – not 'inferior … to the overwhelming majority of other studies'.

In this context Pfizer noted that GlaxoSmithKline had selected one quote from Ferrari *et al* suggesting that 'pain free and sustained pain free rates in the [Pfizer] comparator studies versus eletriptan [were low]'. Pfizer would not review the evidence on this point because the Clinical Summary made no comparator claim regarding the two clinical outcomes 'pain free' and 'sustained pain free'. Furthermore, neither pain free nor sustained pain free were used as a priori primary outcome measures in either the two Pfizer studies, nor in any of the sumatriptan studies reported in Ferrari *et al*.

Despite conclusive validation of the Pfizer head-to-head comparator trials by Ferrari *et al* GlaxoSmithKline attempted to rebut this evidence by submitting a figure in its appeal which suggested 'the relative importance of means and ranges when comparing across studies'. This figure was, in Pfizer's view, inaccurate and misleading because it was not based on the available data. It showed the upper tail of 'Formulation A' barely overlapping with the lower tail of Formulation B' with a claim that: 'overlap of absolute ranges does not necessarily indicate equivalence'.

Pfizer provided a figure that accurately displayed two bell-shaped curves that were based on actual Imigran data (ie, means and 95% confidence intervals) from both the Pfizer-sponsored studies in the Clinical Summary and from Ferrari *et al*. The overlap was substantial, and the difference between the two means (2.5%) was clinically trivial, especially in the light of the fact that the therapeutic gain across placebo-controlled studies of Imigran ranged from a low of 17%, to a high of 40%. Pfizer stated that it was clear from this figure that encapsulation did not (in the words of GlaxoSmithKline) cause a 'marked and consistent difference in efficacy'.

There were marked differences from study to study (>20%) in headache response rates (and therapeutic gain) for oral Imigran. However, it must be emphasized again: these differences occurred in studies in which Imigran was not encapsulated, and so the between-study differences in headache response were not attributable to encapsulation.

Because of these wide differences in efficacy for Imigran, the reliability of a meta-analysis depended on having a sufficient number of controlled studies of similar design. This was the case for the 100mg dose, but not for the 50mg dose, where there were only five published studies which differed greatly in their designs and in some of the clinical characteristics of the patients being studied. These differences tended to 'average out' if a large enough number of studies were included in a meta-analysis, but this was not quite the case with Imigran 50mg. The clinical implication of this was that Ferrari *et al* could not provide strong and reliable 'balance of the evidence' information for Imigran 50mg in contrast to the 100mg dose.

Therapeutic gain: the 'balance of the evidence'

Pfizer noted that in its appeal GlaxoSmithKline had presented figures in an attempt to suggest that the 'balance of the evidence' showed encapsulated Imigran to be inferior in its ability to achieve a headache response at 2 hours. Pfizer contended that GlaxoSmithKline's definition of 'balance of the evidence' was based on a subgroup of selectively chosen articles. This stood in contrast to the comprehensive results reported by Ferrari *et al*.

GlaxoSmithKline's appeal included a figure which it presented, and discussed at length, in the original

complaint. As Pfizer summarized in its original response, both figures were based on a selective and inappropriate choice of studies. Pfizer listed studies which GlaxoSmithKline chose not to include as well as examples of studies that it did include, but inappropriately. These latter studies were not placebo controlled, despite the fact that the International Headache Society clinical trials guidelines explicitly stated that evaluation of migraine efficacy required an appropriate placebo control. GlaxoSmithKline had established its own criteria. By GlaxoSmithKline standards, placebo-controlled studies might be excluded from consideration, but comparator studies were acceptable, even if they contained no placebo control at all. Despite use of these new study inclusion criteria to create one of the figures GlaxoSmithKline was still only able to show a difference in terms of uncorrected headache response at 2 hours. To do so GlaxoSmithKline must ignore therapeutic gain, which was the scientifically accepted standard method used to compare efficacy across studies.

Independent confirmation of Relpax superiority over Imigran

The debate regarding the two figures in the appeal was made moot by the publication of Ferrari *et al* which, as Pfizer had noted, included all known published and unpublished studies of oral Imigran, and to which GlaxoSmithKline contributed its data. Pfizer requested that GlaxoSmithKline accept the meta-analysis as the new comprehensive gold standard, and desist from presenting various smaller subgroups of studies for discussion.

In addition to establishing the clinical equivalence of encapsulated vs non-encapsulated Imigran (as Pfizer had previously summarized), Ferrari *et al* also provided strongly supportive confirmation of the comparative results of the Pfizer-sponsored head-to-head trials. Both Relpax 40mg and 80mg were superior to Imigran 100mg. As Pfizer discussed above, the results of the meta-analysis could not be as definitive regarding Imigran 50mg because of the smaller number of available studies. As a consequence, the 95% confidence intervals for Imigran 50mg were more extensively overlapping, especially with the therapeutic gain achieved by Relpax 40mg. More definitive external validation of the superiority of Relpax 40mg (compared to Imigran 50mg) must await the completion of additional controlled trials.

The best data that evidence-based medical practice could hope for was the following: efficacy results from two or more head-to-head, placebo-controlled comparator trials that were confirmed by a meta-analysis of both published and unpublished studies. This 'gold standard' had been fully achieved for Relpax vs Imigran 100mg, and partially achieved vs the 50mg dose (with further corroborative studies needed).

Conclusion

In conclusion, Pfizer's original response to GlaxoSmithKline's complaint provided data that confirmed the bioequivalence of Pfizer's encapsulated formulation of Imigran, as well as its clinical equivalence.

This response to GlaxoSmithKline's appeal presented further evidence documenting the clinical equivalence of encapsulated Imigran. Pfizer had briefly summarized data showing that the headache response, and therapeutic gain, on unencapsulated Imigran was highly variable, and that this variability in response was greater than 30% and occurred across multiple studies in which encapsulation was not used. Furthermore, Ferrari *et al* definitively established that there was no dose-response curve for the 50mg vs 100mg dose of Imigran. E_{max} data provided a scientific understanding of why dose increases above 50mg did not yield any additional increases in efficacy. It could therefore be concluded that neither dose nor encapsulation could account for the variability in headache response (and therapeutic gain) for oral Imigran. This wide variability in response could be accounted for by differences, from study-to-study, in baseline patient characteristics, and in various other aspects of study design.

Pfizer had discussed how the only fully valid and accepted method of controlling for patient variables that drove differences in treatment response was to perform head-to-head comparator studies with high internal validity. Pfizer had conducted these head-to-head comparator trials, and the results showed Relpax to be superior to Imigran 50mg and 100mg. Pfizer strongly believed that because Pfizer-encapsulated Imigran had been demonstrated to be bioequivalent and clinically equivalent, the efficacy results obtained in the head-to-head comparator results as presented in the Clinical Summary were valid. Ferrari *et al* provided a definitive and independent confirmation of the superior efficacy of Relpax 80mg, and a tentative confirmation of the superiority of the 40mg dose.

For the reasons summarized above Pfizer believed that GlaxoSmithKline had not made a credible and scientifically persuasive argument that the data presented by Pfizer in the Clinical Summary in question were biased and not consistent with the weight of the available data worldwide. For this reason Pfizer believed that GlaxoSmithKline's appeal was without merit.

FURTHER COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline noted that in its appeal it had stated that overlapping efficacy ranges did not necessarily indicate equivalence. Indeed, Pfizer in its response to the appeal conceded that the mean therapeutic gain for encapsulated Imigran was less than that for the non-encapsulated form. At issue then, was the extent of this difference. Pfizer used a mean therapeutic gain for non-encapsulated Imigran of 29% (Ferrari *et al*) and contrasted this with a therapeutic gain of 26.5% for non-encapsulated Imigran, averaged from two of Pfizer's three comparative studies. GlaxoSmithKline believed that these data had been selected to minimise the difference in efficacy evident between the two formulations.

Therapeutic gain for non-encapsulated Imigran

In the eletriptan clinical summary, the most persuasive argument for superior efficacy of eletriptan

over Imigran was that of the pooled data on page 5. This showed a therapeutic gain for encapsulated Imigran 50mg of 22%, and encapsulated Imigran 100mg of 23%.

In its most recent submission, Pfizer had ignored this pooled data, and instead used only the average of the 100mg data to give a therapeutic gain for encapsulated Imigran 100mg of 26.5%. Interestingly, if the same technique was used for encapsulated Imigran 50mg, the average therapeutic gain would be only 17%.

Clause 7.2 of the Code stated that comparisons in promotional material must be fair, accurate and not mislead directly or by implication. In this regard the key question in relation to the Pfizer comparative studies was whether a study of encapsulated Imigran against non-encapsulated eletriptan was a fair comparison, capable of substantiating the claim of consistently superior relief compared to Imigran.

Pfizer had accepted that the true issue at the heart of this case was whether encapsulation reduced the efficacy of Imigran. Therefore the only way that one could determine whether the eletriptan comparative studies were a fair comparison was by consideration of the comparative efficacy of encapsulated Imigran seen in these studies with that of non-encapsulated Imigran from other studies. GlaxoSmithKline believed that the marked difference in efficacy seen with encapsulated Imigran compared with that of non-encapsulated Imigran raised significant doubt about the validity of these studies and their ability to substantiate claims of superiority for eletriptan over that of the marketed formulation of Imigran. A scientifically robust and fair comparison of Imigran and eletriptan would encapsulate both products or encapsulate neither. In the absence of such a study, GlaxoSmithKline did not believe that a claim for clinical superiority of eletriptan over Imigran could be substantiated.

GlaxoSmithKline noted that Pfizer had made many references to pharmacokinetic data, the most relevant of which GlaxoSmithKline would address below. However, as the EMEA noted, these were simply proxy measures of clinical equivalence. The crux of the case concerned whether there was a difference in efficacy between the encapsulated and non-encapsulated formulations, and whether the use of these data was misleading and unrepresentative of the balance of currently available evidence.

1) Efficacy

In its ruling the Panel pointed out that the range of therapeutic gains for the encapsulated form of Imigran 100mg from the Pfizer studies (22-31%) was not dissimilar to the mean therapeutic gain reported by Tfelt-Hansen in his review of 20 Imigran studies (32%).

Therapeutic gain for non-encapsulated Imigran

GlaxoSmithKline agreed that Ferrari *et al* was a useful source of information on the therapeutic gain for Imigran, and indeed had referred to it in its appeal. However, whilst comprehensive, it was only part of the full balance of evidence that should be reviewed. A key issue with Ferrari *et al* was that the therapeutic gain for Imigran was calculated including data from the three studies conducted by Pfizer which used encapsulated Imigran. As GlaxoSmithKline pointed out in its appeal, encapsulation reduced the efficacy of Imigran and therefore the therapeutic gain reported by Ferrari *et al* was likely to be an underestimate. Indeed, it was the lowest mean therapeutic gain seen in meta-analyses – the majority of studies showed a value of 32-33%. This assessment was further supported by other independent opinion.

Contrary to Pfizer's response, Ferrari *et al* did not 'definitively confirm' eletriptan superiority. Eletriptan 40mg was not found to be consistently superior to Imigran 50mg or 100mg.

To summarise, the prescriber, on reviewing the data presented in the clinical summary, would be given the impression that eletriptan 40mg and 80mg were significantly more effective than Imigran 50mg or 100mg from the pooled analysis presented in the graph on page 5. Comparison of the mean therapeutic gain data for encapsulated Imigran from this graph with that of non-encapsulated Imigran from all independent analysis showed a marked difference in efficacy for encapsulated Imigran.

2) Pharmacokinetics

Central to the pharmacokinetic argument was the fact that the rate of absorption ie the rate of appearance of the drug in the blood and subsequent increase of systemic drug concentration, was a significant factor in determining the early response rates of a migraine product. Evidence suggested that this rate was delayed when Imigran was encapsulated.

C_{max}

The Pfizer response to the appeal relied on comparison of the maximal plasma concentration (C_{max}) data as an indicator of equivalence between the encapsulated and the non-encapsulated forms of Imigran. GlaxoSmithKline did not dispute the fact that the C_{max} for both forms was similar. However, Pfizer had missed the crux of the pharmacokinetic issue which was that both Pfizer and GlaxoSmithKline pharmacokinetic studies suggested that encapsulation reduced the rate of absorption over the first 2 hours after dosing. There was therefore less medicine exposure when headache relief was measured at 2 hours. The maximum plasma concentration achieved after dosing (which occurred later with encapsulation) was therefore not directly relevant to this consideration.

GlaxoSmithKline noted that Pfizer had discounted the 21% AUC_{0-2} reduction with encapsulation by applying this percentage decrease to C_{max} values and suggesting that the plasma level attained after this percentage decrease was above a suggested notional concentration necessary to provide a maximal response. As noted above C_{max} was not a directly relevant indicator of the rate and extent of the absorption of a medicine during the first 2 hours after dosing. Further it was not valid to apply a percentage

decrease seen with one parameter (AUC_{0-2}) to another parameter (C_{max}).

GlaxoSmithKline reiterated that these data suggested that it was the rate of absorption – how fast the medicine got on board over the first two hours after dosing – which was an important determinant of the efficacy of encapsulated and non-encapsulated forms of Imigran.

Encapsulation method

GlaxoSmithKline noted that the Panel had accepted Pfizer's argument that its method of encapsulation of Imigran was different to that in the GlaxoSmithKline pharmacokinetic studies and therefore the GlaxoSmithKline data demonstrating delayed absorption for the encapsulated formulation was not acceptable.

GlaxoSmithKline noted that its appeal described that the method of encapsulation used by Pfizer also delayed the absorption of Imigran, reducing the AUC_{0-2} by 21%. GlaxoSmithKline noted that Pfizer's response to its appeal did not mention the method of encapsulation as a key point for consideration, but rather accepted that there was a reduction in AUC_{0-2} of 21% with the encapsulated formulation.

3) Dose response

GlaxoSmithKline noted that Pfizer had suggested that Imigran did not have a dose response relationship, and hence was insensitive to small differences in plasma concentrations. This was not an accurate statement. There was a clear and acknowledged dose response for the tablet formulation. Imigran 25mg was significantly less effective than Imigran 50mg and 100mg. It was for this very reason that the 25mg dose was not licensed in the UK – it was clearly less effective than the 50mg dose, but with a similar tolerability profile.

Furthermore, the presence or absence of a dose-response curve for Imigran was not relevant to this issue. Encapsulating any dose was likely to shift the dose response curve downwards, reducing the maximal response. A key determinant of the validity of this hypothesis would be a comparison of the efficacy of the encapsulated dose, with that of the non-encapsulated dose. In the case of Imigran, GlaxoSmithKline maintained that this efficacy was reduced when Imigran was encapsulated.

In summary, GlaxoSmithKline believed that there was sufficient evidence to throw considerable doubt on the Pfizer claim that a study of encapsulated Imigran against non-encapsulated eletriptan was a fair comparison, and that results from these studies were capable of substantiating a claim of superior efficacy for eletriptan over the marketed formulation of Imigran.

APPEAL BOARD RULING

The Appeal Board noted that the claim at issue that Relpax 'Consistently demonstrated superior relief of migraine headache compared with sumatriptan' related to headache response at 2 hours postdose. The head-to-head trials from which the data were taken had involved the use of encapsulated sumatriptan. The basis of the complaint was that the encapsulation of the sumatriptan resulted in a lower than expected response to the medicine. Milton *et al*, which had been used to demonstrate the bioequivalence of the encapsulated sumatriptan with the marketed (non-encapsulated) formulation, had calculated the area under the plasma concentration-time curve (AUC) from 0 to infinity as one of its primary measures. The Appeal Board noted the Pfizer representatives' submission at the hearing that the study was not powered to detect differences in the pharmacokinetics of the two forms of sumatriptan between 0 and 2 hours. The Appeal Board noted Pfizer's view that the maximum observed plasma concentrations, C_{max}, for the encapsulated and non-encapsulated Imigran were equivalent. It also noted the extensive pharmacokinetic data supplied by Pfizer. GlaxoSmithKline had done a limited post hoc analysis of the Milton *et al* data and estimated that between 0 and 2 hours there was a 16-21% decrease in the AUC for encapsulated sumatriptan compared to the non-encapsulated formulation, thus suggesting that encapsulation of sumatriptan reduced its absorption in the first 2 hours post-dose. Such a reduction in the AUC_{0-2}, while not proven by GlaxoSmithKline, was equally not excluded by Pfizer's response.

The Appeal Board noted that in migraine therapy it was the acute response to a medicine which was important; this was reflected in the efficacy studies in which headache response at 2 hours postdose was the prime efficacy criterion. The Appeal Board noted that there was no corresponding pharmacokinetic data provided by Pfizer to prove that encapsulated sumatriptan was bioequivalent to the marketed product over this time period. The Appeal Board considered that it had not been sufficiently demonstrated that encapsulated sumatriptan would not affect response to treatment over 0 to 2 hours. In that regard the Appeal Board considered that the claim was misleading and a breach of Clause 7.2 of the Code was ruled. The appeal was successful.

2 Figures illustrating a comparison of Relpax and sumatriptan: significance compared with placebo

COMPLAINT

GlaxoSmithKline stated that by the side of each of the figures in the clinical summary comparing Relpax with sumatriptan there was a statement that all patients who received Relpax experienced significantly greater relief compared with placebo. As there was no such statement for sumatriptan, the implication was that the difference between sumatriptan and placebo did not reach statistical significance. GlaxoSmithKline believed that not including the significance value for sumatriptan, or at least a statement to the effect that this was not analysed in the study, was misleading and a breach of Clause 7.8.

RESPONSE

Pfizer stated that sumatriptan was included as an

active comparator in the Pfizer studies and was accepted as an established, effective agent as it had been shown to be superior to placebo in numerous previous studies. For that reason, the statistical analysis plans for these studies did not include a planned comparison between sumatriptan and placebo. It was assumed that readers would be well aware of sumatriptan's superiority over placebo; it was certainly not Pfizer's intention to mislead them in this respect. Pfizer did not therefore believe that the clinical summary was misleading in this respect, or that it infringed Clause 7.8. However, GlaxoSmithKline's interpretation of the above figures was noted and Pfizer would take this into account in preparing future materials.

PANEL RULING

Pages 3-5 of the Relpax Clinical Summary presented data comparing the efficacy of Relpax vs sumatriptan. The heading to page 4 was 'Consistently demonstrated superior relief of migraine headache compared with sumatriptan'. In this context the Panel considered that a positive statement about Relpax would imply the opposite was true for sumatriptan. Beside each bar chart showing headache response at 2 hours post-dose was the statement 'All patients who received Relpax experienced significantly greater relief compared to placebo'. The Panel considered that this implied that patients who received sumatriptan had not experienced significantly greater relief compared to placebo. Although the clinical trials had not statistically analysed the difference in response between placebo and sumatriptan the Panel considered that the statement about Relpax gave a misleading impression about the efficacy of sumatriptan as alleged and the bar charts were thus misleading in this regard. A breach of Clause 7.8 was ruled.

3 Prescribing information

COMPLAINT

GlaxoSmithKline stated that on the front page of the clinical summary there was a statement to the effect that full prescribing information could be found inside the pocket. However, the inside pocket contained the Relpax SPC which could easily be removed. GlaxoSmithKline understood that prescribing information should form part of the promotional material and must not be separate from it and therefore it believed this to be a breach of Clause 4.1.

RESPONSE

Pfizer acknowledged that the prescribing information was present at the end of the document in the form of the SPC inserted into a plastic sleeve wallet. Pfizer believed that this was an integral part of the document and therefore not in breach of Clause 4.1. However, the point raised by GlaxoSmithKline had been noted and Pfizer would in future endeavour to incorporate the prescribing information as actual text within items such as this. In response to a request for further information Pfizer confirmed that at the time of the World Congress on Neurology in mid-June 2001, Relpax was approved for use throughout Europe.

PANEL RULING

The Panel noted that Clause 4.1 of the Code stated, *inter alia*, that the prescribing information must form part of the promotional material and must not be separate from it.

The Relpax Clinical Summary booklet contained, in a pocket on the inside back page, a loose copy of the SPC. The Panel noted that the prescribing information as listed in Clause 4.2 of the Code was not the same as the SPC. The prescribing information required a succinct statement of the information in the SPC relating to the dosage, method of use relevant to the indications in the advertisement and where not otherwise obvious, the route of administration. Similarly the information about relevant side-effects, precautions and contra-indications should be given in an abbreviated form. The prescribing information should also contain details of cost; a matter not included at all in an SPC.

The Panel considered that the prescribing information for Relpax had not been provided in the Clinical Summary booklet as required. A breach of Clause 4.1 was ruled.

Complaint received **15 August 2001**

Case completed **7 March 2002**

CASES AUTH/1247/11/01 and AUTH/1248/11/01

SHIRE v PFIZER and PHARMACIA

Summary of COX-2 review

Shire complained about a summary of a review article on the use of COX-2 inhibitors in arthritis sponsored jointly by Pfizer and Pharmacia. By way of introduction, a subtitle to the summary, which had been prepared by the companies, stated that it assessed the evidence base relating to the COX-2 specific drugs celecoxib and rofecoxib, as well as the COX-2 selective NSAIDs [non-steroidal anti-inflammatory drugs] etodolac and meloxicam. Pfizer and Pharmacia co-promoted Celebrex (celecoxib) and Shire supplied Lodine SR (etodolac).

Shire stated that the term 'specific' in the subtitle was not used elsewhere in the summary itself nor in the full article and was inconsistent with the Celebrex and Vioxx (rofecoxib) summaries of product characteristics (SPCs), which referred to 'selective' inhibition. Shire also wished to raise the issue of the attempt in the summary to differentiate these two from the other two COX-2 selective inhibitors on inconsistent evidence not supported by the SPCs. Scientifically, specific meant restricted in application, effect etc to a particular structure, function etc; ie in this context, no inhibition of the COX-1 enzyme. Vane and Warner (2000) had raised this issue by stating, *inter alia*, that: " 'Specific' is a term that pharmacologists use with great exactitude …. As far as COX-2 inhibitors are concerned, the term 'specific' should be abandoned". Etodolac (and meloxicam) had been shown to be more COX-2 selective than Celebrex in some enzyme assays (Warner *et al* 1999) and Shire remained consistent with the SPC by not referring to etodolac as 'COX-2 specific'. The full review article discussed results from Warner *et al* grouping celecoxib, etodolac and meloxicam together in terms of COX-2 over COX-1 selectivity. However these results, which were inconsistent with the description of celecoxib as a COX-2 *specific* inhibitor, were not mentioned in the summary. The National Institute for Clinical Excellence (NICE) in its recent guidance referred to all four as 'COX-2 selective inhibitors'. There was a potential safety issue surrounding this nomenclature. Lack of inhibition of COX-1 implied lack of gastrointestinal (GI) toxicity. All the COX-2 selective inhibitors (including Celebrex) caused some GI toxicity.

The Panel noted that the original review, entitled 'COX-2 inhibitors in arthritis. A critical appraisal', considered the evidence that selective COX-2 inhibitors offered clinically significant advantages over older NSAIDs in the treatment of arthritis, whether etodolac and meloxicam were viable alternatives to products developed as selective COX-2 inhibitors and contrasted celecoxib and rofecoxib with a view to aiding selection of a single COX-2 inhibitor for formulary inclusion. The review described NSAIDs by reference to their COX-2 selectivity, rather than specificity. The summary of the review article, produced by Pharmacia and Pfizer, similarly referred to COX-2 selectivity, save in the subtitle which read 'The review assesses the evidence base relating to the COX-2 specific drugs celecoxib and rofecoxib, as well as the COX-2 selective NSAIDs etodolac and meloxicam'. The Celebrex SPC stated that it was an oral active selective inhibitor of cyclo-oxygenase-2 (COX-2) within the therapeutic dose range (200-400mg daily). The Vioxx SPC described it as an 'orally active cyclo-oxygenase-2 (COX-2) selective inhibitor within the clinical dose range'. Neither SPC described its product as specific in relation to COX-2 inhibition. The Panel noted Pharmacia and Pfizer's submission that Celebrex and rofecoxib were referred to as COX-2 specific in a wide range of scientific literature and noted the studies submitted in this regard. The NICE guidance stated that 'There is wide variation in the reported COX-II selectivity of the NSAIDs, as assessed by different assay techniques, and therefore classification of these agents according to their selectivity remains problematic. Celecoxib and rofecoxib, two recently introduced COX-II inhibitors, are often classified as 'COX-II specific agents' due to claims of higher COX-II selectivity compared to the more established NSAIDs, meloxicam and etodolac, which are often referred to as 'COX-II selective'. This guidance refers to all four drugs as 'COX-II selective inhibitors'.'

The Panel noted the statement in the NICE guidance about the description of products as COX-2 selective or COX-2 specific. This was a complex area; NSAIDs presented with varying degrees of selectivity. In the Panel's view specificity was an absolute; in this case it inferred exclusive inhibition of COX-2 with no inhibition at all of COX-1. Neither Celebrex nor Vioxx were described in their respective SPCs as COX-2 specific; the review article referred to selectivity rather than specificity. The summary in question used both terms. The Panel considered that on balance the summary produced by the companies was thus inconsistent with the Celebrex SPC on this point and the Panel ruled a breach of the Code.

A breach of the Code was ruled because the summary did not include the prescribing information even though it was promotional material.

Shire stated that the full article claimed to be a critical appraisal of COX-2 inhibitors but in Shire's opinion this summary was in part highly selective in its content. The information and comparisons in the summary were not balanced. In the third bullet point on page 1 'Celecoxib and rofecoxib have been shown to be highly selective inhibitors of COX-2 in a number of assay systems' there was no reference to etodolac and meloxicam as COX-2 selective inhibitors.

The Panel noted that the review article in a section entitled 'Pharmacology COX-2 inhibition' discussed issues surrounding the clinically relevant measurement of COX-2 inhibition and concluded that studies indicated that 'if COX-2 selectivity is a useful attribute then celecoxib and rofecoxib should have safety advantages over older NSAIDs and these may be shared, to a greater or lesser extent, by

meloxicam and etodolac'. Whilst the summary subtitle referred to etodolac and meloxicam as COX-2 selective NSAIDs this was immediately preceded by a description of celecoxib and rofecoxib as COX-2 specific. The third bullet point referred to celecoxib and rofecoxib as highly selective inhibitors. None of the bullet points referred to the selectivity of etodolac and meloxicam. The Panel considered that this omission placed etodolac and meloxicam in an unfavourable light; it would raise doubts in the readers' minds about the medicines' selectivity. Whilst the original review noted differences between the products' selectivity profiles, the Panel considered that the failure to reflect this discussion in relation to etodolac and meloxicam meant that the summary was not a fair reflection of the review in this regard. A breach of the Code was ruled.

On page 2 the first bullet point was 'Celecoxib is licensed for use in the symptomatic management of rheumatoid arthritis (RA) whilst rofecoxib does not have an RA licence. Both drugs have been shown in large scale, well conducted trials to be as effective in relieving the symptoms of RA as traditional NSAIDs'. Shire noted that there was no mention of the fact that both etodolac and meloxicam had licences for rheumatoid arthritis (RA).

The Panel noted that the review article gave the licensed indications for each medicine. The licensed indications for etodolac and the various presentations of meloxicam were not identical. In relation to the treatment of rheumatoid arthritis etodolac was indicated for acute or long-term use and meloxicam was indicated, *inter alia*, for the long-term symptomatic treatment. The bullet point at issue clearly stated the licensed indications (and efficacy) for celecoxib and rofecoxib in relation to rheumatoid arthritis. The equivalent information for etodolac and meloxicam was not provided. The following bullet point referred solely to the efficacy of etodolac and meloxicam in the treatment of rheumatoid arthritis and made critical comment on the etodolac studies due to their small sample size. The Panel considered that the failure to clearly state the products' licensed indications meant that the summary was unfair in this regard and a breach of the Code was ruled.

Shire noted that the final bullet point stated that when considering which of the four medicines reviewed to recommend, a number of points needed to be considered; these were then listed in bullet point format. However, in the third stab point 'the drugs have different licensed indications – celecoxib has broader licensed indications (OA & RA) than rofecoxib (OA)', there was no mention of the broad licensed indications of etodolac (the same as celecoxib – shown in the full review article). Further, the fifth bullet point 'celecoxib is less expensive than rofecoxib at the doses used most commonly in osteoarthritis (in the USA)', although accurately quoting an item from the full review, did not quote the relative expenses of etodolac and meloxicam relative to the 'coxibs'. Such additions would be highly relevant to the argument.

The Panel noted that the final bullet point listed five stab points to be considered when deciding which of the four medicines to recommend. The third stab point read 'the drugs have different licensed indications – celecoxib has broader licensed indications (OA & RA) than rofecoxib (OA)'. Etodolac held a similarly broad licence in osteoarthritis and rheumatoid arthritis. The Panel considered that the information presented was not sufficiently balanced, the equivalent information for etodolac had not been presented. The stab point gave the impression that celecoxib had the broadest indication of each product examined in the review and that was not so. The stab point was misleading in this regard. A breach of the Code was ruled.

The fifth stab point read 'Celecoxib is less expensive than rofecoxib at the doses used most commonly in osteoarthritis (in the USA)'. The Panel noted that the review concluded that the price difference between celecoxib and rofecoxib in the treatment of osteoarthritis was one of the factors likely to influence pharmacists and formulary committees when selecting which agent to use. The review discussed the relative costs of COX-2 medicines in relation to cost effective expenditure on risk reduction and acquisition cost, focussing primarily on celecoxib and rofecoxib. The Panel considered that the summary was not balanced in this regard. Equivalent information regarding the relative cost of etodolac and meloxicam had not been provided. A breach of the Code was ruled.

Shire noted that the summary mentioned several safety issues favouring celecoxib but failed to quote the statement in the review article that 'giving low-dose aspirin as a cardioprotective agent alongside celecoxib has been shown to reduce [in fact eliminate –NICE guidance] its margin of GI safety over older NSAIDs'. Since many patients recommended for treatment with celecoxib received concomitant low-dose aspirin Shire believed that this observation was important and should have been included in the summary.

The Panel noted that the second bullet point in the summary stated that 'COX-2 inhibitors have been developed to provide the therapeutic properties of traditional NSAIDs but with fewer side effects'. Further bullet points compared celecoxib favourably with rofecoxib in relation to gastrointestinal tolerability and renal events. The review article stated that celecoxib and rofecoxib were unlikely to have any protective effect against myocardial infarction and that this was a potential problem since giving low dose aspirin as a cardioprotective agent alongside celecoxib had been shown to reduce its margin of GI safety over older NSAIDs (Silverstein *et al*, 2000). The companies had submitted that according to its SPC, Celebrex and aspirin could be co-prescribed. The summary discussed the treatment of arthritis and GI side effects and also referred to renal events; it did not discuss cardioprotective issues. The Panel did not consider that the failure to mention the effect of the concomitant prescription of aspirin as a cardioprotective agent meant that the summary was misleading as alleged and no breach of the Code was ruled.

Shire stated that the summary of the review article had been produced without the author's

involvement. Shire questioned whether some of the claims or views contained in the summary represented his current views, particularly as the summary had been handed out to GPs since issue of the NICE guidance on COX-2 selective inhibitors in July 2001.

The Panel noted that the heading of the summary was such that a reader would expect it to be a fair and accurate representation of the author's views as expressed in the original review. The Panel noted its rulings above on the content of the summary. The Panel had no evidence before it concerning the author's present views. Pfizer and Pharmacia had submitted that the summary had been withdrawn because the author had been unhappy for his name to be so closely associated with a piece of promotional material. No breach of the Code was ruled.

Shire Pharmaceuticals Ltd complained about a summary of a review article on the use of COX-2 inhibitors in arthritis sponsored jointly by Pfizer Limited and Pharmacia Limited. By way of introduction, a subtitle to the summary stated that it assessed the evidence base relating to the COX-2 specific drugs celecoxib and rofecoxib, as well as the COX-2 selective NSAIDs [non-steroidal anti-inflammatory drugs] etodolac and meloxicam. The companies submitted a joint response. The summary was provided to regional and specialist sales representatives responsible for detailing to customers with budgetary decision making responsibilities and may have been made available to general sales representatives on an individual basis. It was provided in two presentation formats, a CD ROM and within a folder pack. Pfizer and Pharmacia co-promoted Celebrex and Shire produced Lodine SR (etodolac).

The Panel noted that the summary provided by Shire differed from that provided by Pharmacia and Pfizer. The summary provided by Shire was four pages long whereas the version provided by Pharmacia and Pfizer was six pages long; the type size and font spacing also differed. The summary provided by the respondent companies bore a reference 83605b and included prescribing information for Celebrex, neither of which appeared on the summary provided by Shire. The statement 'Supported with an educational grant from Pharmacia and Pfizer Ltd' appeared, in the version supplied by Shire, at the bottom of the final page (page 4) beneath the list of references and in the respondent companies' version at the top of page 5 above the prescribing information. The Panel considered this case in relation to the version complained about by Shire, a copy of which had been supplied to the respondent companies when they were notified of the complaint.

1 The term 'specific'

COMPLAINT

Shire stated that the author of the article to which the summary related, had written to Shire to advise that he had had no input to the summary, a fact confirmed by Pharmacia. A copy of the full article – which was supported by an educational grant from Pharmacia and Pfizer – was forwarded to Shire by Pharmacia on request. Shire had asked Pharmacia when or where the article was likely to be published but it had been unable to supply Shire with this information. The summary and the original article were provided.

Shire regarded this company summary of an independent unpublished article sponsored by the two companies as promotional.

The term 'specific' in the subtitle to the summary was not used elsewhere in the summary itself nor in the full article and was inconsistent with the Celebrex and Vioxx summaries of product characteristics (SPCs), which referred to 'selective' inhibition. Shire alleged breaches of Clauses 11.2 and 3.2.

Shire realised that this might seem a pedantic point but it wished to raise the issue of the attempt in this summary to differentiate these two from the other two COX-2 selective inhibitors on inconsistent evidence not supported by the SPCs. Scientifically, 'specific' meant 'restricted in application, effect etc to a particular structure, function etc' (Dorlands Illustrated Medical Dictionary 23rd Edn), ie in this context, no inhibition of the COX-1 enzyme. Vane and Warner (2000) had raised this issue by stating, *inter alia*, that: "'Specific' is a term that pharmacologists use with great exactitude …. As far as COX-2 inhibitors are concerned, the term 'specific' should be abandoned". Etodolac (and meloxicam) had been shown to be more COX-2 selective than Celebrex in some enzyme assays (Warner *et al* 1999) and Shire remained consistent with the SPC by not referring to etodolac as 'COX-2 specific'.

The full review article on page 6 discussed results from Warner *et al* (1999), grouping celecoxib, etodolac and meloxicam together in terms of COX-2 over COX-1 selectivity. However these results, which were inconsistent with the description of Celebrex as a COX-2 *specific* inhibitor, were not mentioned in the summary.

The National Institute for Clinical Excellence (NICE) in its recent Guidance No 27 (paragraph 3.3) referred to all four medicines as 'COX-2 selective inhibitors'.

Shire stated that there was a potential safety issue surrounding this nomenclature. Lack of inhibition of COX-1 implied lack of gastrointestinal (GI) toxicity. All the COX-2 selective inhibitors (including Celebrex) caused some GI toxicity.

RESPONSE

The companies stated that in September of this year, following informal discussions between Pharmacia and Pfizer, Shire and the author of the review article, they decided to withdraw the summary article because the companies became aware that the author was unhappy for his name to be so closely associated with what was a piece of promotional material.

The companies were, however, prepared to defend their piece against the other allegations levelled by Shire.

The term 'specific' only appeared as part of a supplement to the title. Celebrex and rofecoxib were

referred to as 'COX-2 specific' in a wide range of scientific literature, a point that was made in the NICE guidance (section 3.3). It was therefore accepted nomenclature and its use did not constitute a breach of the Code.

It had been suggested that:

'To be categorized as a specific COX-2 inhibitor, a compound must show therapeutic benefit comparable to that of a conventional NSAID with no meaningful effect on the gastric mucosa that can be ascribed to COX-1 inhibition and no inhibition of COX-1 mediated platelet function in clinical trials' (Lipsky *et al* 1998).

It was accepted by many experts that a medicine had fulfilled this criteria if it demonstrated, throughout the full therapeutic range, a superior GI safety to agents inhibiting COX-1 (NSAIDs) and no affect on platelet function. This definition fitted with the available clinical data on Celebrex.

Studies in healthy volunteers showed that both celecoxib and rofecoxib had no detectable effect on platelet function With respect to GI ulcer complications, robust evidence existed from a meta-analysis that celecoxib did, in comparison to NSAIDs, demonstrate placebo levels of upper GI ulcer complications across its licensed therapeutic range. In addition, when celecoxib was administered at twice the maximum licensed dose (Silverstein *et al* 2000), the Celebrex Long-Term Arthritis Safety Study (CLASS), a significant reduction was demonstrated in symptomatic ulcers and ulcer complications. Recent data from Goldstein *et al* (2001), a large study in osteoarthritis (SUCCESS1), suggested an >80% reduction in ulcer complications versus traditional NSAIDs when Celebrex was used within its licensed dose range. Similar data was available for rofecoxib.

The companies refuted the suggestion that referring to Celebrex and rofecoxib as 'specific' might be viewed as a potential safety issue and therefore felt vindicated in their use of the term 'specific' in reference to Celebrex and contended that this did not constitute a breach of the Code.

In its letter, Shire had made reference to Warner *et al* commenting that celecoxib, etodolac and meloxicam had similar selectivity for the COX-2 enzyme. Shire had chosen not to include discussion of the time dependent nature of Celebrex's selectivity for COX-2 as discussed in this and other work. Depending on the assay system used, celecoxib had an 8-3200 fold selectivity for the COX-2 enzyme over that for COX-1, with a figure of 375 most commonly quoted in the literature. Given the degree of variation in assay techniques, the companies considered it was inappropriate to derive meaningful conclusions regarding COX-2 selectivity from a single study. In keeping with published opinion, they used the term 'specific' with reference to the proven reductions in clinical events seen with both Celebrex and rofecoxib. The review article made reference to the variability in COX-2 selectivity and concluded that available data for COX-2 selectivity was more robust for celecoxib and rofecoxib than for meloxicam and etodolac.

PANEL RULING

The Panel noted that the original review, entitled 'COX-2 inhibitors in arthritis. A critical appraisal', considered the evidence that selective COX-2 inhibitors offered clinically significant advantages over older NSAIDs in the treatment of arthritis; whether etodolac and meloxicam were viable alternatives to products developed as selective COX-2 inhibitors and contrasted celecoxib and rofecoxib with a view to aiding selection of a single COX-2 inhibitor for formulary inclusion. The review described NSAIDs by reference to their COX-2 selectivity, rather than specificity.

The Panel noted that the summary of the review article, produced by Pharmacia and Pfizer, similarly referred to COX-2 selectivity, save in the subtitle which read 'The review assesses the evidence base relating to the COX-2 specific drugs celecoxib and rofecoxib, as well as the COX-2 selective NSAIDs etodolac and meloxicam'.

The Panel noted that according to Section 5.1 of its SPC, headed Pharmacodynamics, Celebrex was 'an oral active selective inhibitor of cyclo-oxygenase-2 (COX-2) within the therapeutic dose range (200-400mg daily). No statistically significant inhibition of COX-1 (assessed as *ex vivo* inhibition of thromboxane B2 [TxB2] formation) was observed in this dose range in healthy volunteers'. Section 5.1 of the Vioxx SPC headed Pharmacodynamic properties described Vioxx as an 'orally active cyclo-oxygenase-2 (COX-2) selective inhibitor within the clinical dose range'. This section stated that 'Statistically significant inhibition of COX-1 has not been documented in humans with any dose of rofecoxib'. Neither SPC described its product as specific in relation to COX-2 inhibition. The Panel noted Pharmacia and Pfizer's submission that Celebrex and rofecoxib were referred to as COX-2 specific in a wide range of scientific literature and noted the studies submitted in this regard.

Paragraph 3.3 of the NICE guidance No.27 stated that 'There is wide variation in the reported COX-II selectivity of the NSAIDs, as assessed by different assay techniques, and therefore classification of these agents according to their selectivity remains problematic. Celecoxib and rofecoxib, two recently introduced COX-II inhibitors, are often classified as 'COX-II specific agents' due to claims of higher COX-II selectivity compared to the more established NSAIDs, meloxicam and etodolac, which are often referred to as 'COX-II selective'. This guidance refers to all four drugs as 'COX-II selective inhibitors'.'

The Panel noted Shire's submission that there was a potential safety issue as lack of inhibition of COX-1 implied lack of GI toxicity. Section 4.4 of the Celebrex SPC 'Special warnings and special precautions for use' stated that 'Upper gastrointestinal perforations, ulcers or bleeds (PUBs) have occurred in patients treated with celecoxib. Therefore caution should be taken in patients with a history of gastrointestinal disease, such as ulceration and inflammatory conditions or in patients at special risk'. Section 4.8 'Undesirable effects' listed gastrointestinal events as common (>1%) abdominal pain, diarrhoea, dyspepsia,

and flatulence; uncommon (1%-0.1%) constipation, eructation, gastritis, stomatitis and vomiting; rare (<0.1%) duodenal, gastric and oesophageal ulceration, dysphagia, intestinal perforation, oesophagitis and melaena.

The Panel noted that Vane and Warner (2000) discussed the nomenclature for COX-2 inhibitors and stated that there was a strong correlation between reduced GI damage with celecoxib, rofecoxib and meloxicam and their sparing COX-1 effects. The authors noted that many degrees of COX-2 selectivity had been reported and as a consequence scientific reports and advertisements were littered with adjectival descriptions of COX-2 inhibitors; some tidying up was called for. The authors further noted that 'Specific was a term that pharmacologists use with great exactitude. It should not be redefined by marketeers to cover only therapeutic concentrations at which a particular drug inhibits COX-2 but not COX-1'. The article concluded that all medicines with well proven lower toxicity on the GI tract should be grouped together as selective COX-2 inhibitors.

The Panel noted the statement in the NICE guidance about the description of products as COX-2 selective or COX-2 specific. The Panel considered that this was a complex area; NSAIDs presented with varying degrees of selectivity. In the Panel's view specificity was an absolute; in this case it inferred exclusive inhibition of COX-2 with no inhibition at all of COX-1. Neither Celebrex nor Vioxx were described in their respective SPCs as COX-2 specific; the review article referred to selectivity rather than specificity. The summary in question used both terms. The Panel considered that on balance the summary produced by the companies was thus inconsistent with the Celebrex SPC on this point and the Panel ruled a breach of Clause 3.2.

Shire had also alleged a breach of Clause 11.2 which applied to quotations. The subtitle of the summary was not an actual quotation from the original article. Clause 11.2 was thus not applicable. No breach of Clause 11.2 was ruled.

2 Prescribing Information

COMPLAINT

Shire believed that this summary was promotional for Celebrex and the prescribing information should be included. The prescribing information was not attached to the two copies of the summary that Shire had seen. A breach of Clause 4.1 of the Code was alleged.

RESPONSE

Pharmacia and Pfizer stated that it would be noted from the copies of the original summary article which were provided that the prescribing information was in fact appended. It appeared that this information had been detached from the copy of the summary article supplied by Shire to the Authority. Pharmacia and Pfizer therefore submitted that Clause 4.1 of the Code had not been breached.

PANEL RULING

The Panel noted its comments above regarding the differences between the two versions of the document at issue; the version of the summary provided by Shire did not contain prescribing information. The Panel noted Pharmacia and Pfizer's submission that prescribing information was appended but considered that this related to the version which they had provided in response to the complaint. The Panel noted that there were two presentation formats. The Panel had no evidence before it that prescribing information was appended to the summary provided by Shire. Clause 4.1 required prescribing information to appear on all promotional material and a breach of that clause was ruled.

When considering this point the Panel also noted that both versions of the summary failed to satisfy further requirements of Clause 4 in that neither featured the non-proprietary name of the medicine or the list of active ingredients adjacent to the most prominent display of the brand name as required by Clause 4.3. The summary provided by the respondent companies was six pages long but did not contain a clear reference as to where the prescribing information could be found as required by Clause 4.8 of the Code. The Panel asked that the companies be advised of its views in this regard.

3a Page 1: third bullet point 'Celecoxib and rofecoxib have been shown to be highly selective inhibitors of COX-2 in a number of assay systems'

COMPLAINT

Shire stated that the full article claimed to be a critical appraisal of COX-2 inhibitors but in Shire's opinion this summary was in part highly selective in its content. Shire alleged that the information and comparisons in the summary were not balanced and were therefore in breach of Clause 7.2 of the Code. In this bullet point there was no reference to etodolac and meloxicam as COX-2 selective inhibitors (Shire referred to its submission at point 1 above and to the upper half of page 6 of the review article).

RESPONSE

The companies refuted the suggestion that there was data for meloxicam and etodolac showing a high degree of COX-2 selectivity. Celebrex had been shown to be between 8-3200 fold more selective for the COX-2 enzyme than the COX-1, with a figure of 375 most commonly quoted. Selectivity for rofecoxib was quoted as being between 35-800. In contrast the selectivity attributed to etodolac had a range of between 1.2 – 23 derived from various assay systems. The corresponding figures for meloxicam were 3 – 77. The companies therefore asserted that celecoxib and rofecoxib had been shown to be highly selective for the COX-2 enzyme in a number of assay systems. In contrast both etodolac and meloxicam had been demonstrated to have a lower degree of selectivity and as such could not be considered as highly selective COX-2 inhibitors. This was consistent with

the review article which concluded that: 'If COX-2 selectivity is a useful attribute, then celecoxib and rofecoxib should have safety advantages over older NSAIDs and these may be shared, to a greater or lesser extent, by meloxicam and etodolac'.

PANEL RULING

The Panel noted that the summary featured thirteen bullet points which purported to summarize the original review. The third bullet point read 'Celecoxib and rofecoxib have been shown to be highly selective inhibitors of COX-2 in a number of assay systems'.

The review article in a section entitled 'Pharmacology COX-2 inhibition', discussed issues surrounding the clinically relevant measurement of COX-2 inhibition and concluded that studies indicated that 'if COX-2 selectivity is a useful attribute then celecoxib and rofecoxib should have safety advantages over older NSAIDs and these may be shared, to a greater or lesser extent, by meloxicam and etodolac'.

The Panel noted that whilst the summary heading referred to etodolac and meloxicam as COX-2 selective NSAIDs this was immediately preceded by a description of Celebrex and Vioxx as COX-2 specific. The third bullet point referred to celecoxib and rofecoxib as highly selective inhibitors. None of the bullet points referred to the selectivity of etodolac and meloxicam.

The Panel considered that this omission placed etodolac and meloxicam in an unfavourable light; it would raise doubts in the readers' minds about the medicines' selectivity. Whilst the original review noted differences between the products' selectivity profiles the Panel considered that the failure to reflect this discussion in relation to etodolac and meloxicam meant that the summary was not a fair reflection of the review in this regard. A breach of Clause 7.2 was ruled.

3b Page 2: first bullet point 'Celecoxib is licensed for use in the symptomatic management of rheumatoid arthritis (RA) whilst rofecoxib does not have an RA licence. Both drugs have been shown in large scale, well conducted trials to be as effective in relieving the symptoms of RA as traditional NSAIDs.'

COMPLAINT

Shire noted that in this bullet point there was no mention of the fact that both etodolac and meloxicam had licences for rheumatoid arthritis (RA). These should be obvious inclusions in a balanced summary and were shown in table 4 of the review article. A breach of Clause 7.2 was alleged.

RESPONSE

The companies referred to the second bullet point on the second page of the summary article which read 'Etodolac and meloxicam have been shown to be as efficacious as traditional NSAIDs in the treatment of RA. Again the etodolac studies have been criticised due to small sample size. There is relatively limited meloxicam data in RA and again it is questioned whether meloxicam is as effective as other agents at the 7.5mg dose'. It clearly stated that both meloxicam and etodolac had been shown to be efficacious in rheumatoid arthritis. As such this did not constitute a breach of the Code.

PANEL RULING

Table 4 of the review article set out the licensed indications of each medicine. The Panel noted that according to their SPCs the licensed indications for etodolac and the various presentations of meloxicam were not identical. In relation to the treatment of rheumatoid arthritis, etodolac was indicated for acute or long-term use in rheumatoid arthritis and meloxicam was indicated, *inter alia*, for the long-term symptomatic treatment of rheumatoid arthritis. The bullet point at issue clearly stated the licensed indications (and efficacy) for celecoxib and rofecoxib in relation to rheumatoid arthritis. The equivalent information for etodolac and meloxicam was not provided. The following bullet point referred solely to the efficacy of etodolac and meloxicam in the treatment of rheumatoid arthritis and made critical comment on the etodolac studies due to their small sample size. The Panel considered that the failure to clearly state the products' licensed indications meant that the summary was unfair in this regard. A breach of Clause 7.2 was ruled.

3c Page 2: final bullet point

COMPLAINT

Shire noted that this bullet point stated that when considering which of the four medicines reviewed to recommend, a number of points needed to be considered; these were then listed in stab point format. However, in the third stab point 'the drugs have different licensed indications – celecoxib has broader licensed indications (OA & RA) than rofecoxib (OA)', there was no mention of the broad licensed indications of etodolac (the same as celecoxib – shown in table 4 of the review article). Further, the fifth stab point 'celecoxib is less expensive than rofecoxib at the doses used most commonly in osteoarthritis (in the USA)', although accurately quoting an item from the full review, did not quote the relative expenses of etodolac and meloxicam relative to the 'coxibs'. Such additions would be highly relevant to the argument. A breach of Clause 7.2 was alleged.

RESPONSE

Pharmacia and Pfizer stated that the licensed indications for etodolac were no broader than for celecoxib. The example of RA for celecoxib, but not rofecoxib, was given as an example to the statement that 'the drugs have different licensed indications. Given this was a brief summary it could not reasonably be expected to include all the considerations contained within the review article. The summary contained neither factual inaccuracies, nor was misleading with respect to the licensed

indications of etodolac or meloxicam. Similarly the relative costs of celecoxib and rofecoxib were only used as an example for the statement 'when considering which of the four drugs to recommend a number of points need to be considered'. Again this was factually correct and was not intended to mislead.

PANEL RULING

The Panel noted that the final bullet point listed five stab points to be considered when considering which of the four medicines to recommend. The third stab point read 'the drugs have different licensed indications – celecoxib has broader licensed indications (OA & RA) than rofecoxib (OA)'. The Panel noted that etodolac held a similarly broad licence in osteoarthritis and rheumatoid arthritis. The Panel considered that the information presented was not sufficiently balanced, the equivalent information for etodolac had not been presented. The stab point gave the impression that celecoxib had the broadest indication of each product examined in the review and that was not so. The stab point was misleading in this regard. A breach of Clause 7.2 was ruled.

The fifth stab point read 'Celecoxib is less expensive than rofecoxib at the doses used most commonly in osteoarthritis (in the USA)'. The Panel noted that the review concluded that the price difference between celecoxib and rofecoxib in the treatment of osteoarthritis was one of the factors likely to influence pharmacists and formulary committees when selecting which agent to use. The review discussed the relative costs of COX-2 medicines in relation to cost effective expenditure on risk reduction and acquisition cost, focussing primarily on celecoxib and rofecoxib.

The Panel considered that the summary was not balanced in this regard. Equivalent information regarding the relative cost of etodolac and meloxicam had not been provided. A breach of Clause 7.2 was ruled.

3d Safety

COMPLAINT

Shire noted that the summary mentioned several safety issues favouring celecoxib but failed to quote the statement on page 16 of the review that 'giving low-dose aspirin as a cardioprotective agent alongside celecoxib has been shown to reduce [in fact eliminate – see NICE Guidance paragraph 4.8] its margin of GI safety over older NSAIDs'; since many patients recommended for treatment with celecoxib received concomitant low-dose aspirin Shire believed that this observation was important and should have been included in the summary. A breach of Clause 7.2 was alleged.

RESPONSE

Pfizer and Pharmacia stated that the SPC for Celebrex stated that aspirin might be co-prescribed. There was no prospective, sufficiently powered study that had definitely documented a reduction in the safety profile of celecoxib when co-prescribed with low dose aspirin. As such the piece was consistent with the SPC and the recommendations of the licensing authority.

The companies therefore contended that the omission referred to by Shire was not in breach of the Code.

PANEL RULING

The Panel noted that the second bullet point in the summary stated that 'COX-2 inhibitors have been developed to provide the therapeutic properties of traditional NSAIDs but with fewer side effects'. Further stab points compared celecoxib favourably with rofecoxib in relation to gastrointestinal tolerability and renal events.

The Panel further noted the original review stated that celecoxib and rofecoxib were unlikely to have any protective effect against myocardial infarction and that this was a potential problem since giving low dose aspirin as a cardioprotective agent alongside celecoxib had been shown to reduce its margin of GI safety over older NSAIDs (Silverstein *et al*, 2000). The Panel noted the companies' submission that according to its SPC, Celebrex and aspirin could be co-prescribed. The Panel noted that the summary discussed the treatment of arthritis and GI side effects and also referred to renal events; it did not discuss cardioprotective issues. The Panel did not consider that the failure to mention the effect of the concomitant prescription of aspirin as a cardioprotective agent meant that the summary was misleading as alleged. No breach of Clause 7.2 was ruled.

4 Clauses 11.2 and 11.4

COMPLAINT

Shire stated that the summary of the review had been produced without the author's involvement. Shire questioned whether some of the claims or views contained in this summary represented the author's current views, particularly since the summary had been handed out to GPs since issue of the comprehensive NICE Guidance on COX-2 selective inhibitors in July 2001. Shire alleged breaches of Clauses 11.2 and 11.4 regarding the claims in this summary.

RESPONSE

Pharmacia and Pfizer believed that the summary article accurately represented the original review on the basis of the commentary and information provided in points 1 and 3 above and as such did not accept that any breach of Clause 11.2 of the Code had been committed.

The companies noted that the views of an author might change over time and that, in retrospect, it would have been best practice to obtain the written consent of the author for the particular use of the article and period of use. As the use consisted of the preparation of a summary of the original, the need to

obtain a consent was not self-evident. However, upon being alerted to the potential sensitivity, Pharmacia and Pfizer co-operated with Shire and the author in promptly withdrawing the summary article.

The companies believed that Shire had taken an inappropriate position in failing to acknowledge withdrawal of the summary article (as a result of discussion and agreement with Pharmacia and Pfizer) when making its formal complaint to the Authority. Recourse to the Authority on this issue was unnecessary and contrary to a spirit of co-operation which might have resulted in an early resolution of the complaint.

PANEL RULING

The Panel noted that Clause 11.2 stated that 'Quotations from medical and scientific literature, or from personal communications must accurately reflect the meaning of the author'. The summary did not contain any quotations from the original article; it summarised its content but did not quote from it. No breach of Clause 11.2 was ruled.

Clause 11.4 required the utmost care to be taken to avoid ascribing claims or views to authors when these no longer represented their current views. The Panel noted that the heading of the summary was such that a reader would expect it to be a fair and accurate representation of the author's views as expressed in the original review. The Panel noted its rulings above on the content of the summary. The Panel had no evidence before it concerning the author's present views. Pfizer and Pharmacia had submitted that the summary had been withdrawn because the author had been unhappy for his name to be so closely associated with a piece of promotional material. No breach of Clause 11.4 was thus ruled.

The Panel noted that Pfizer and Pharmacia had withdrawn the summary. This did not preclude the submission of a complaint as suggested.

Complaint received **5 November 2001**

Case completed **28 January 2002**

CASE AUTH/1249/11/01

GLAXOSMITHKLINE v AVENTIS PASTEUR MSD

Promotion of Viatim

GlaxoSmithKline complained about a leavepiece and a mailing for Viatim (combined Vi polysaccharide typhoid and inactivated hepatitis A vaccine) issued by Aventis Pasteur MSD, and also complained about misleading statements which it alleged had been made by Aventis Pasteur MSD representatives. Viatim was presented as two separate suspensions for injection in a pre-filled, dual-chamber syringe.

The claim 'The only combination vaccine to offer fast seroconversion (14 days) to both hepatitis A and typhoid fever' appeared in the leavepiece and the claim 'Ideal for last minute travellers – Viatim can be given just 2 weeks before travelling whereas the other combination vaccine should preferably be given at least 4 weeks before' appeared in the mailing. GlaxoSmithKline stated that there were only two combination vaccines for typhoid and hepatitis A available in the UK; its product Hepatyrix and Viatim. These claims implied that Hepatyrix did not produce seroconversion within 14 days, and was therefore inferior to Viatim in this respect. The Viatim summary of product characteristics (SPC) stated that 14 days after vaccination, 86.4% of subjects had seroconverted against typhoid and 95.6% had seroconverted against hepatitis A. The corresponding figures in the Hepatyrix SPC were 97.5% for typhoid and 89.8% for hepatitis A. There was no suggestion from the available data to support the claim that Viatim acted more rapidly than Hepatyrix. The claims implied that a head-to-head study had demonstrated a significant difference between the two vaccines; however, no such study had been carried out.

The Viatim SPC stated 'Viatim should be administered to subjects at risk of exposure to hepatitis A and typhoid fever, but protective levels may not be reached until 14 days after administration of the vaccine'. The corresponding statement in the Hepatyrix SPC read 'The vaccine should be given at least two weeks prior to exposure to typhoid and preferably one month prior to risk of exposure to hepatitis A'. It was possible that Aventis Pasteur MSD was basing its claims on the differences between these two statements. However, the Viatim SPC statement was based directly on the results of Overbosch *et al* (2001), whereas the Hepatyrix SPC statement was intended to reflect best vaccination practice for the optimal protection of patients – it did not imply a slower rate of seroconversion. Indeed, the Viatim SPC statement could be considered misleading as it implied that 100% of Viatim vaccinees would be adequately protected against typhoid and hepatitis A from 14 days after vaccination. This was clearly not the case as 14 days after vaccination, only 86.4% of subjects had seroconverted against typhoid and 95.6% against hepatitis A.

The Panel noted that a comparison of the data in the SPCs showed that at 14 days a greater percentage of patients were protected against typhoid with Hepatyrix than with Viatim (97.5% v 86.4% respectively) but the position with regard to protection against hepatitis A was reversed (89.8% v 95.6% respectively). At 28 days, again a greater percentage of patients were protected against typhoid with Hepatyrix than with Viatim (96% v 90.3% respectively) and almost equal percentages were protected against hepatitis A (99% v 99.7% respectively). The Panel noted that such data had not come from a head-to-head comparison of the two vaccines and so the statistical significance of the differences was not known.

In the Panel's view, most readers would assume that the claim that Viatim was 'The only combination vaccine to offer fast seroconversion (14 days) to both hepatitis A and typhoid fever' meant that protection against hepatitis A and typhoid from any other combination vaccine took longer than 14 days to develop. There was no data to show that Viatim offered significantly faster protection against hepatitis A and typhoid than Hepatyrix, the only other combination vaccine. The Panel considered that the claim was misleading and that it could not be substantiated. Breaches of the Code were ruled.

The Viatim SPC stated that 'Viatim should be administered to subjects at risk of exposure to hepatitis A and typhoid fever, but protective levels may not be reached until 14 days after administration of the vaccine'. The same section of the Hepatyrix SPC stated that 'The vaccine should be given at least two weeks prior to risk of exposure to typhoid and preferably one month prior to risk of exposure to hepatitis A'. The Panel noted its comments above with regard to the speed and degree of protection to hepatitis A and typhoid fever offered by each product. In the Panel's view most readers would assume that the claim 'Ideal for last minute travellers – Viatim can be given just two weeks before travelling whereas the other combination vaccine should preferably be given at least 4 weeks before' meant that Hepatyrix could not be administered two weeks prior to travelling. This was not so. In addition the claim implied that Hepatyrix had to be given at least 4 weeks before travelling whereas the SPC stated that it should be given 'preferably one month prior to risk of exposure to hepatitis A'. The Panel considered that the claim was misleading with regard to the dosage schedule of Hepatyrix and that it could not be substantiated. Breaches of the Code were ruled.

GlaxoSmithKline noted that Hepatyrix and Viatim were presented differently. Viatim was in a dual chamber syringe, with both vaccines separated until they were mixed together, immediately prior to injection. Hepatyrix had both vaccines already mixed together in the same syringe, which simplified the administration process. Aventis Pasteur MSD had stated that it initially attempted to develop a mixed formulation of its separate typhoid and hepatitis A vaccines (Typhim and Avaxim), but it encountered the problem of a reduced immune response against typhoid compared to that obtained with Typhim given as a single vaccination.

The claim 'Dual chamber technology preserves the integrity of both vaccines' appeared in the leavepiece and might be interpreted simply as a statement of fact about Viatim. However, GlaxoSmithKline was aware that Aventis Pasteur MSD representatives were using it with customers in such a way as to cast doubt on the stability or 'integrity' of Hepatyrix, saying that the typhoid component 'interferes with' the hepatitis A component. In order to reinforce this message, customers were reminded that GlaxoSmithKline had carried out a stock management exercise earlier in 2001 to ensure that only batches of Hepatyrix aged 18 months (ie 6 months less than the 24 months shelf life) were used. This was in fact carried out as a precautionary measure, following some QA test results that indicated a possible loss of potency after 18 months. However, the test results had since been shown to be due to the validity of the test assay itself rather than the stability of Hepatyrix, and the issue had been completely resolved. GlaxoSmithKline therefore believed that the claim was being interpreted to imply that vaccine 'integrity' in its mixed formulation of Hepatyrix might be compromised and alleged that this was misleading. GlaxoSmithKline also alleged that some Aventis Pasteur MSD representatives had been making misleading claims.

The Panel noted that, with regard to 'Viatim positioning', the representatives' briefing material stated that as the innovative syringe technology used with Viatim kept the two component parts of the vaccine separate until just before administration, the intrinsic characteristics of each, such as tolerability, immunogenicity and speed of seroconversion, were thus fully preserved. One of the product's benefits was 'Combined reliability and performance of two well known vaccines, as a result of the dual-chamber syringe technology'. One of the 'key messages' was that as the dual-chamber syringe for Viatim might seem more complicated than the presentation of Hepatyrix 'It is therefore imperative to link the syringe technology used in Viatim to the speed of seroconversion (need to make a direct comparison between Viatim SPC and Hepatyrix SPC) as it demonstrates several benefits of Viatim'. In the Panel's view this implied that the dual-chamber syringe resulted in clinical advantages for Viatim. In a question and answer section of the briefing material entitled 'Objections to using Viatim vs Hepatyrix' the first question was 'Why is Viatim not pre-mixed like Hepatyrix?'. Representatives were told that initial Viatim trials, using a pre-mixed vaccine, showed that interference between the two components occurred which resulted in a sub-optimal response to the typhoid vaccine. Therefore to maintain the reliability and optimal performance of the individual vaccines the two were kept separate in the dual chamber syringe. This ensured the maximum response to both components. In the Panel's view, without a statement to the contrary, this question and answer and other aspects of the briefing material implied that there might be interference between the two components of Hepatyrix resulting in a vaccine which was less effective than Viatim.

The Panel noted Aventis Pasteur MSD's submission that its representatives had been informed that there was no data to suggest an interference between the two components of Hepatyrix. The company had also reminded its representatives that to cast doubt on the stability of Hepatyrix would be misleading.

The Panel considered that the briefing material supplied, by not including clear statements to the contrary, cast doubt on the stability and clinical effectiveness of Hepatyrix compared with Viatim because Hepatyrix was present as a single suspension for injection and not in a dual-chamber syringe like Viatim. The Panel considered that in this regard the briefing material was misleading and likely to lead to a breach of the Code. A breach of the Code was ruled.

A similar claim in the leavepiece 'Dual chamber technology preserves integrity of both vaccines' was the second of four stabpoints. The first and last stabpoints, 'The only combination vaccine to offer fast seroconversion (14 days) to both hepatitis A and typhoid fever' and 'Competitively priced compared with the other combination vaccine' respectively, in effect compared Viatim favourably with Hepatyrix. In the Panel's view it was not unreasonable to assume that the claim in question would also be seen as a favourable comparison versus Hepatyrix. The Panel noted its comments above regarding the briefing material and considered that the claim, although true, was misleading within the context in which it had been used. A breach of the Code was ruled.

Upon appeal of these two rulings by Aventis Pasteur MSD, the Appeal Board noted that during the development of Viatim it had become necessary to present the product in a dual chamber syringe to prevent the loss of potency of the typhoid component which had been observed to occur over time with the original vaccine formulated as a pre-mixed suspension for injection. The claim 'Dual chamber technology preserves integrity of both vaccines' was thus a true statement about Viatim. This, however, appeared in the leavepiece as the second of four stabpoints, the first and last of which clearly, and favourably, compared Viatim with Hepatyrix. Given the context in which the claim appeared the Appeal Board considered that some readers would assume that it too was a comparison with Hepatyrix, the implication being that, as Hepatyrix was pre-mixed in a single chamber syringe, then the integrity of both of its vaccines was not preserved. The Appeal Board considered that given the context in which it had been used the claim was misleading and upheld the Panel's ruling of a breach of the Code.

With regard to the representatives briefing materials, the Appeal Board noted, *inter alia*, that in the section entitled 'Objections to using Viatim vs Hepatyrix' representatives were told that Aventis Pasteur MSD had originally developed a pre-mixed vaccine, similar to Hepatyrix, but that clinical trials had shown that interference between the two components occurred when in a fully liquid formulation resulting in a sub-optimal response to the typhoid component. Therefore to maintain the reliability and optimal performance of the individual vaccines the two were kept separate in a dual chamber syringe. The Appeal Board considered that reference to Hepatyrix in a discussion of the stability problems encountered during the initial development of Viatim as a pre-mixed vaccine threw doubts on to the stability of Hepatyrix and implied that the presentation of that product might also result in a sub-optimal response to the typhoid component.

The Appeal Board considered that the difference in presentation of Hepatyrix and Viatim was likely to be an issue with customers. The problems encountered during the early development of Viatim and the subsequent need for a dual chamber syringe were specific to that product. The Appeal Board did not consider that the briefing material adequately addressed the issue; the need for a dual chamber syringe for Viatim appeared to be presented as an advantage compared to the single chamber syringe of Hepatyrix and there was no data before the Appeal Board in this regard. The Appeal Board considered that the briefing material was misleading and likely to lead to a breach of the Code. The Panel's ruling of a breach of the Code was upheld.

GlaxoSmithKline complained about a leavepiece (ref 4006977) and a mailing (ref 2428/0601A) for Viatim (combined Vi polysaccharide typhoid and inactivated hepatitis A vaccine) issued by Aventis Pasteur MSD Ltd, and also complained about misleading statements which it alleged had been made by Aventis Pasteur MSD representatives. Viatim was presented as two separate suspensions for injection in a pre-filled, dual-chamber syringe.

Aventis Pasteur MSD stated that the leavepiece primarily explained how to use the dual-chamber syringe but also provided a few key points about the product. It had been sent out with orders of Viatim and had been left with customers by sales representatives. It was still in use but with the date of preparation added as this had been omitted due to an administrative error. The mailing had been sent out with another item to one practice nurse in each GP surgery in England and Wales.

A Claim 'The only combination vaccine to offer fast seroconversion (14 days) to both hepatitis A and typhoid fever'

This claim appeared in the leavepiece.

B Claim 'Ideal for last minute travellers – Viatim can be given just 2 weeks before travelling whereas the other combination vaccine should preferably be given at least 4 weeks before'

This claim appeared in the mailing.

COMPLAINT

GlaxoSmithKline stated that there were currently only two combination vaccines for typhoid and hepatitis A available in the UK; these were its product Hepatyrix and Viatim.

The above claims implied that Hepatyrix did not produce seroconversion within 14 days, and was therefore inferior to Viatim in this respect.

The summary of product characteristics (SPC) for Viatim stated that 14 days after vaccination, 86.4% of subjects had seroconverted against typhoid and 95.6% had seroconverted against hepatitis A. The corresponding figures in the Hepatyrix SPC were 97.5% for typhoid and 89.8% for hepatitis A.

GlaxoSmithKline provided a table giving a summary of seroconversion rates at days 14 and 28 for the two vaccines, from the available study data. GlaxoSmithKline stated that as could be seen from the table, there was no suggestion from the available data to support the claim that Viatim acted more rapidly than Hepatyrix. The claims implied that a head-to-head study comparing Hepatyrix and Viatim had demonstrated a significant difference between the two vaccines; however, no such study had been carried out..

The Viatim SPC stated: 'Viatim should be administered to subjects at risk of exposure to hepatitis A and typhoid fever, but protective levels may not be reached until 14 days after administration of the vaccine.' The corresponding statement in the Hepatyrix SPC read: 'The vaccine should be given at least two weeks prior to exposure to typhoid and preferably one month prior to risk of exposure to hepatitis A.'

It was possible that Aventis Pasteur MSD was basing its claims on the differences between these two statements. However, the Viatim SPC statement was based directly on the results of Overbosch *et al* (2001), whereas the Hepatyrix SPC statement was intended to reflect best vaccination practice for the optimal protection of patients – it did not imply a slower rate of seroconversion. Indeed, the Viatim SPC statement could be considered misleading to health professionals as it implied that 100% of Viatim vaccinees would be adequately protected against typhoid and hepatitis A from 14 days after vaccination. This was clearly not the case as 14 days after vaccination, only 86.4% of subjects had seroconverted against typhoid and 95.6% against hepatitis A.

GlaxoSmithKline therefore alleged that the above claims were misleading, in breach of Clause 7.2 of the Code, and incapable of substantiation, in breach of Clause 7.4.

RESPONSE

Aventis Pasteur MSD noted that these claims were based directly upon the SPCs for the two products:

The SPC for Hepatyrix stated, in section 4.2, 'The vaccine should be given at least two weeks prior to risk of exposure to typhoid and preferably one month prior to risk of exposure to hepatitis A'. The corresponding statement from the Viatim SPC read 'Viatim should be administered to subjects at risk of exposure to hepatitis A and typhoid fever, but protective levels may not be reached until 14 days after administration of the vaccine'.

It was therefore clear from the SPCs that Hepatyrix should preferably be given one month before exposure to hepatitis A whereas protection by Viatim was conferred in 14 days for both hepatitis A and typhoid. The claims were therefore substantiated.

GlaxoSmithKline quoted a number of different seroconversion rates for the two vaccines from the SPCs and from other published sources. The claims at issue did not imply that data from any head-to-head study existed. Indeed, it was disingenuous to try to make comparisons in the way that GlaxoSmithKline had done – it was for this reason that Aventis Pasteur MSD did not do so. Antibody response to the typhoid component of Viatim in clinical trials was measured serologically using a standardized quantitative assay reporting weight-based units (µg/ml). Studies of Hepatyrix, on the other hand, had used an ELISA assay reporting in arbitrary units (EU/ml). It was therefore entirely inappropriate to compare these results directly since they were derived in different studies, at different times, in different laboratories using different methodologies.

Conversely a different indirect comparison might be more fruitful. Clinical trials with Viatim demonstrated that the immune response to Viatim was equivalent to the separate components, Avaxim (hepatitis A) and Typhim Vi (typhoid fever), given concomitantly at separate injection sites (Viatim SPC section 5.1). Similarly, clinical trials with Hepatyrix demonstrated that the immune response to Hepatyrix was equivalent to GlaxoSmithKline's monovalent vaccines, Havrix (hepatitis A) and Typherix (typhoid fever), given concomitantly at separate injection sites. Therefore, since Viatim was essentially a combination of Avaxim and Typhim Vi (in a dual chamber syringe), and Hepatyrix was essentially a combination of Havrix and Typherix in a fully liquid presentation, a comparison of the two manufacturers' monovalent vaccines, where they had been directly compared in the same study, was relevant.

A direct comparison of Avaxim and Havrix was performed as part of the clinical development of Avaxim and had been published (Zuckerman *et al* 1997). This clearly demonstrated a statistically significantly higher ($p<0.01$) seroconversion rate two weeks after receipt of Avaxim (95.7%) compared to Havrix (87.1%). These were very similar to the seroconversion rates seen after Viatim and Hepatyrix respectively.

A direct comparison of Typhim Vi and Typherix was alluded to in section 5.1 of the Typherix SPC. However a direct comparative study of the two vaccines in children, performed by GlaxoSmithKline and employing its ELISA assay, had been published (Cordero-Yap *et al* 1999). This paper stated 'Both vaccines induced high, identical seroconversion rates in the initially seronegative subjects. Also the GMTs were similar'. It was therefore clear that both products induced very similar seroconversion rates. The seroconversion rate (measured by ELISA) observed in this study, for Typhim Vi, was very similar to the seroconversion rate (measured by ELISA) seen after Hepatyrix.

These studies demonstrated that both manufacturers' typhoid fever vaccines were similarly immunogenic

(when assessed using the same assay). The hepatitis A vaccines, however, differed in that Avaxim (also used to formulate Viatim) induced seroconversion more rapidly than Havrix. The same situation pertained to the combination vaccines and was reflected in the differing wording in their respective SPCs.

In conclusion, the claims at issue were factually based upon statements in the SPCs for the two products. Direct comparisons of the seroconversion rates for the two combination products were invalid. The claims were therefore in breach of neither Clause 7.2 nor Clause 7.4.

PANEL RULING

Section 5.1, Pharmacodynamic Properties, of the Viatim SPC gave details of the seroconversion rates (percentage of patients) for hepatitis A and typhoid seen 14 and 28 days after vaccination. The same section of the Hepatyrix SPC gave comparable data although immunity was expressed in terms of seropositivity rates. Although different terms had been used in each SPC, and the methods for determining seroconversion as opposed to seropositivity might be different, the data in each SPC referred to the percentage of patients who would have developed antibodies to hepatitis A and typhoid. The data showed that at 14 days a greater percentage of patients were protected against typhoid with Hepatyrix than with Viatim (97.5% v 86.4% respectively) but the position with regard to protection against hepatitis A was reversed (89.8% v 95.6% respectively). At 28 days, again a greater percentage of patients were protected against typhoid with Hepatyrix than with Viatim (96% v 90.3% respectively) and almost equal percentages were protected against hepatitis A (99% v 99.7% respectively). The Panel noted that such data had not come from a head-to-head comparison of the two vaccines and so the statistical significance of the differences was not known.

In the Panel's view, most readers would assume that the claim that Viatim was 'The only combination vaccine to offer fast seroconversion (14 days) to both hepatitis A and typhoid fever' meant that protection against hepatitis A and typhoid from any other combination vaccine took longer than 14 days to develop. There was no data to show that Viatim offered significantly faster protection against hepatitis A and typhoid than Hepatyrix, the only other combination vaccine. Notwithstanding the fact that the Viatim SPC referred to seroconversion and the Hepatyrix SPC referred to seropositivity, the Panel considered that the claim was misleading and that it could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

Section 4.2, Posology and Method of Administration, of the SPC for Viatim stated that 'Viatim should be administered to subjects at risk of exposure to hepatitis A and typhoid fever, but protective levels may not be reached until 14 days after administration of the vaccine'. The same section of the Hepatyrix SPC stated that 'The vaccine should be given at least two weeks prior to risk of exposure to typhoid and preferably one month prior to risk of exposure to hepatitis A'. The Panel noted its comments above with regard to the speed and degree of protection to hepatitis A and typhoid fever offered by each product.

In the Panel's view most readers would assume that the claim 'Ideal for last minute travellers – Viatim can be given just two weeks before travelling whereas the other combination vaccine should preferably be given at least 4 weeks before' meant that Hepatyrix could not be administered two weeks prior to travelling. This was not so. In addition the claim implied that Hepatyrix had to be given at least 4 weeks before travelling whereas the SPC stated that it should be given 'preferably one month prior to risk of exposure to hepatitis A'. The Panel considered that the claim was misleading with regard to the dosage schedule of Hepatyrix and that it could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

C Claim 'Dual chamber technology preserves the integrity of both vaccines'

This claim appeared in the leavepiece and a similar claim appeared in the mailing.

COMPLAINT

GlaxoSmithKline stated that a difference between Hepatyrix and Viatim was that of presentation. Viatim was presented in a dual chamber syringe, with both vaccines separated until they were mixed together, immediately prior to injection. In contrast to this Hepatyrix was presented with both vaccines already mixed together in the same syringe, which simplified the administration process.

Aventis Pasteur MSD had stated that it initially attempted to develop a mixed formulation of its separate typhoid and hepatitis A vaccines (Typhim and Avaxim), but it encountered the problem of a reduced immune response against typhoid compared to that obtained with Typhim given as a single vaccination.

The claim might be interpreted simply as a statement of fact about Viatim. However, GlaxoSmithKline was aware that Aventis Pasteur MSD representatives were using the statement with customers in such a way as to cast doubt on the stability or 'integrity' of Hepatyrix, saying that the typhoid component 'interferes with' the hepatitis A component. In order to reinforce this message, they were reminding customers about the fact that GlaxoSmithKline carried out a stock management exercise earlier this year to ensure that customers only used batches of Hepatyrix aged 18 months (ie 6 months less than the 24 months shelf life). This was in fact carried out as a precautionary measure, following some QA test results that indicated a possible loss of potency after 18 months. However, the test results had since been shown to be due to the validity of the test assay itself rather than the stability of Hepatyrix, and the issue had been completely resolved.

GlaxoSmithKline had many anecdotal reports of the above, and a written verification from a customer was provided in confidence.

GlaxoSmithKline therefore believed that the claim was being interpreted to imply that vaccine 'integrity' in its mixed formulation of Hepatyrix might be compromised. As such, GlaxoSmithKline alleged that this was misleading, in breach of Clause 7.2. GlaxoSmithKline also alleged that some Aventis Pasteur MSD representatives had been making misleading claims to customers, in breach of Clause 15.

RESPONSE

Aventis Pasteur MSD stated that GlaxoSmithKline was correct in its assumption that this claim was 'simply a statement of fact about Viatim' as was confirmed in previous correspondence with it. The claim had nothing to do with Hepatyrix.

With regard to the activities of Aventis Pasteur MSD sales representatives, this had also been the subject of correspondence with GlaxoSmithKline. During their training on Viatim Aventis Pasteur MSD representatives were informed of the rationale behind the dual chamber presentation, namely to prevent negative interference between the two vaccine components. However they were also informed that there were no data to suggest such an interference with Hepatyrix.

Aventis Pasteur MSD representatives should not be casting doubt on the stability of Hepatyrix and they most certainly had never been advised to do such a thing. Aventis Pasteur MSD did not believe that such activities were occurring. However, the anecdotal evidence presented by GlaxoSmithKline did not allow Aventis Pasteur MSD to investigate this any further. As a precautionary measure it had reiterated that such activities would be misleading, in breach of the Code and would be taken very seriously.

Since the claim was a statement of fact about Viatim, and had nothing to do with Hepatyrix, it was not in breach of Clause 7.2. Nor did Aventis Pasteur MSD believe that its representatives had breached Clause 15. If further information could be provided about the latter it could be investigated in more detail.

Aventis Pasteur MSD provided copies of the representatives' briefing material.

PANEL RULING

The Panel noted that, with regard to 'Viatim positioning', the representatives' briefing material stated that as the innovative syringe technology used with Viatim kept the two component parts of the vaccine separate until just before administration, the intrinsic characteristics of each, such as tolerability, immunogenicity and speed of seroconversion, were thus fully preserved. One of the product's benefits was 'Combined reliability and performance of two well known vaccines, as a result of the dual-chamber syringe technology'. One of the 'key messages' was that as the dual-chamber syringe for Viatim might seem more complicated than the presentation of Hepatyrix 'It is therefore imperative to link the syringe technology used in Viatim to the speed of seroconversion (need to make a direct comparison between Viatim SPC and Hepatyrix SPC) as it demonstrates several benefits of Viatim'. In the Panel's view this statement implied that the dual-chamber syringe resulted in clinical advantages for Viatim. In a question and answer section of the briefing material entitled 'Objections to using Viatim vs Hepatyrix' the first question was 'Why is Viatim not pre-mixed like Hepatyrix?'. Representatives were told that initial Viatim trials, using a pre-mixed vaccine, showed that interference between the two components occurred which resulted in a sub-optimal response to the typhoid vaccine. Therefore to maintain the reliability and optimal performance of the individual vaccines the two were kept separate in the dual chamber syringe. This ensured the maximum response to both components. In the Panel's view, without a statement to the contrary, this question and answer and other aspects of the briefing material implied that there may be interference between the two components of Hepatyrix resulting in a vaccine which was less effective than Viatim.

The Panel noted Aventis Pasteur MSD's submission that its representatives had been informed that there was no data to suggest an interference between the two components of Hepatyrix. The company had also reminded its representatives that to cast doubt on the stability of Hepatyrix would be misleading.

The Panel considered that the briefing material supplied, by not including clear statements to the contrary, cast doubt on the stability and clinical effectiveness of Hepatyrix compared with Viatim because Hepatyrix was present as a single suspension for injection and not in a dual-chamber syringe like Viatim. The Panel considered that in this regard the briefing material was misleading and likely to lead to a breach of the Code. A Breach of Clause 15.9 was ruled.

The claim in the leavepiece 'Dual chamber technology preserves integrity of both vaccines' was the second of four stabpoints. The first and last stabpoints, 'The only combination vaccine to offer fast seroconversion (14 days) to both hepatitis A and typhoid fever' and 'Competitively priced compared with the other combination vaccine' respectively, in effect compared Viatim favourably with Hepatyrix. In the Panel's view it was not unreasonable to assume that the claim in question would also be seen as a favourable comparison versus Hepatyrix. The Panel noted its comments above regarding the briefing material and considered that the claim, although true, was misleading within the context in which it had been used. A breach of Clause 7.2 was ruled.

APPEAL BY AVENTIS PASTEUR MSD

Aventis Pasteur MSD reiterated that its initial attempt to formulate a combined pre-mixed hepatitis A and typhoid vaccine was unsuccessful. This was because of an apparent decrease in immune response to the typhoid component. It was thought that this occurred as a result of a chemical alteration of the typhoid antigen in the syringe when it was in prolonged contact with the hepatitis A component of the combined vaccine. As a result, the product was reformulated in a dual chamber syringe to prevent this happening.

It was therefore important to explain to health professionals the reason for presenting Viatim in a dual chamber syringe. Not to do so would make it hard for them to understand why Viatim required reconstitution whereas Hepatyrix did not.

Aventis Pasteur MSD stated that it was incorrect to state that the claim 'in effect compared Viatim favourably with Hepatyrix', simply because two other bullet points made a comparison with Hepatyrix (which were clear and unambiguous). No comparison was made and none was intended – this was a statement of fact, as was acknowledged by the Panel.

Aventis Pasteur MSD noted that its briefing material, the relevant pages of which had been supplied to the Panel, was entirely factual and explained the rationale behind the dual chamber presentation, namely to prevent negative interference between the two vaccine components. Again, it was incorrect to state that the material 'by not including clear statements to the contrary, cast doubt on the stability and clinical effectiveness of Hepatyrix'. Aventis Pasteur MSD noted that it had provided material to show that its representatives had been reminded that to cast doubt on the stability of Hepatyrix would be misleading.

COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline noted Aventis Pasteur MSD's submission that the claim was simply a statement of fact about Viatim – the company was not attempting to imply that the stability or efficacy of Hepatyrix were compromised by its mixed formulation presentation.

GlaxoSmithKline reiterated that it was aware that Aventis Pasteur MSD representatives had been using the statement with customers in such a way as to cast doubt on the stability or 'integrity' of Hepatyrix. In order to reinforce this message, they were reminding customers that GlaxoSmithKline had carried out a stock management exercise earlier in 2001 to ensure that customers only used batches of Hepatyrix aged 18 months (ie 6 months less than the 24 months shelf life). [This was in fact carried out as a precautionary measure, following some quality assurance test results that indicated a possible loss of potency after 18 months. However, the test results had since been shown to be due to the validity of the test assay itself rather than the stability of Hepatyrix, and the issue had been completely resolved.]

GlaxoSmithKline noted that it had had many anecdotal reports of the above, and a written verification from a customer was submitted with its complaint.

As the Panel had noted, the claim was also being used in some promotional materials as one of a series of stab points, eg 'The only combination vaccine to offer fast seroconversion (14 days) …' and 'Competitively priced compared with the other combination vaccine', which were designed to compare Viatim favourably with Hepatyrix. It was therefore not unreasonable to assume that the claim in question would also be seen as a favourable comparison.

GlaxoSmithKline noted that in their briefing material the representatives were informed that: 'The dual chamber presentation was developed to prevent negative interference between the two vaccine components'. As the Panel had noted, the representatives' briefing material stated: 'With the innovative syringe technology used with Viatim, both these vaccines are contained in the same syringe, but are kept completely separate until just before administration. The intrinsic characteristics of each of the two component vaccines, such as tolerability, immunogenicity and speed of seroconversion, are thus fully preserved'. The briefing material also stated that the benefits Viatim offered to health professionals and travellers were 'Combined reliability and performance of two well known vaccines, as a result of the dual chamber syringe technology'.

GlaxoSmithKline noted that one of the key messages was that, as the dual chamber syringe for Viatim might seem more complicated than Hepatryix, 'It is therefore imperative to link the syringe technology used in Viatim to the speed of seroconversion (need to make a direct comparison between the Viatim SPC and Hepatyrix SPC) as it demonstrates several benefits of Viatim'.

In a question and answer section of the briefing material entitled 'Objections to using Viatim vs Hepatyrix' the first question was 'Why is Viatim not pre-mixed like Hepatyrix?'. Representatives were told that initial Viatim trials, using a pre-mixed vaccine, showed that interference between the two components occurred, which resulted in a sub-optimal response to the typhoid vaccine. Therefore, to maintain the reliability and optimal performance of the individual vaccines, the two were kept separate in the dual chamber syringe. This ensured the maximum response to both components.

GlaxoSmithKline agreed with the Panel's view that, without a statement to the contrary, this question and answer and other aspects of the briefing material implied that there might be an interference between the two components of Hepatyrix. Furthermore, the statement implied that the dual chamber syringe resulted in clinical advantages for Viatim, as it attempted to link the 'syringe technology' directly to the speed of seroconversion (ie efficacy) of the vaccines.

GlaxoSmithKline noted that the Aventis Pasteur MSD representatives were told that there were no data to suggest such an interference with Hepatyrix. 'Aventis Pasteur MSD representatives should not be casting doubt on the stability of Hepatyrix and they most certainly had never been advised to do such a thing'.

GlaxoSmithKline noted that Aventis Pasteur MSD had supplied no evidence whatsoever to support the above assertion. Indeed, its response to GlaxoSmithKline's request for this evidence was as follows: 'This information was imparted orally and, even if it had been available I do not feel that it would be appropriate to supply you with internal company training documents'.

GlaxoSmithKline also noted Aventis Pasteur MSD's comments to GlaxoSmithKline that '… it would be completely understandable for a GP or practice nurse to be concerned about a product, such as Hepatyrix,

which has required two batch recalls for 9 batches of a product over a period of 8 months as a result of an apparent loss of potency … these facts would have a negative impact on the image of almost any product … these are facts for which GlaxoSmithKline not Aventis Pasteur MSD are responsible'.

GlaxoSmithKline stated, as noted above, that the Hepatyrix batch recalls were due to the quality assurance assay results, not the stability of Hepatyrix, and the issue was completely resolved some time ago. However, Aventis Pasteur MSD's comments certainly seemed to imply that its representatives would be expected to respond in the above manner in the 'very likely' event that the subject of 'potency and the batch recalls of Hepatyrix' came up in discussion with customers.

GlaxoSmithKline noted that Aventis Pasteur MSD had stated that it did not believe that such activities were occurring and that the anecdotal evidence presented by GlaxoSmithKline did not allow Aventis Pasteur MSD to investigate this further; if further information could be provided it could be investigated in more detail.

GlaxoSmithKline noted that written confirmation from a customer as to what she had been told by a representative from Aventis Pasteur MSD was submitted with its complaint. The customer specifically requested to remain anonymous as she did not wish to be approached by Aventis Pasteur MSD about this matter; also, she did not want to identify the representative concerned.

In summary, GlaxoSmithKline stated that it agreed with the Panel's rulings that the representatives' briefing materials were in breach of Clause 15.9 of the Code, and the claim in question was misleading, in breach of Clause 7.2.

APPEAL BOARD RULING

The Appeal Board noted that during the development of Viatim it had become necessary to present the product in a dual chamber syringe to prevent the loss of potency of the typhoid component which had been observed to occur over time with the original vaccine formulated as a pre-mixed suspension for injection. The dual chamber syringe was designed for use such that the two component vaccines, typhoid and hepatitis A, only came together immediately before injection. The claim 'Dual chamber technology preserves integrity of both vaccines' was thus a true statement about Viatim. This, however, appeared in the leavepiece as the second of four stabpoints, the first and last of which clearly, and favourably, compared Viatim with Hepatyrix. Given the context in which the claim appeared the Appeal Board considered that some readers would assume that it too was a comparison with Hepatyrix, the implication being that, as Hepatyrix was pre-mixed in a single chamber syringe then the integrity of both of its vaccines was not preserved. The Appeal Board considered that given the context in which it had been used the claim was misleading and upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal on this point was unsuccessful.

With regard to the activity of the representatives the Appeal Board only took into account their written briefing material. Although a customer's letter had been submitted with the complaint from GlaxoSmithKline the identity of the customer had not been revealed to Aventis Pasteur MSD and so the company had been unable to investigate the matter with the representative concerned.

With regard to the representatives briefing material the Appeal Board noted, *inter alia*, that in the section entitled 'Objections to using Viatim vs Hepatyrix' representatives were told that Aventis Pasteur MSD had originally developed a pre-mixed vaccine, similar to Hepatyrix, but that clinical trials had shown that interference between the two components occurred when in a fully liquid formulation resulting in a sub-optimal response to the typhoid component. Therefore to maintain the reliability and optimal performance of the individual vaccines the two were kept separate in a dual chamber syringe. The Appeal Board considered that reference to Hepatyrix in a discussion of the stability problems encountered during the initial development of Viatim as a pre-mixed vaccine threw doubts on to the stability of Hepatyrix and implied that the presentation of that product might also result in a sub-optimal response to the typhoid component.

The Appeal Board considered that the difference in presentation of Hepatyrix and Viatim was likely to be an issue with customers. The problems encountered during the early development of Viatim and the subsequent need for a dual chamber syringe were specific to that product. The Appeal Board did not consider that the briefing material adequately addressed the issue; the need for a dual chamber syringe for Viatim appeared to be presented as an advantage compared to the single chamber syringe of Hepatyrix and there was no data before the Appeal Board in this regard. The Appeal Board considered that the briefing material was misleading and likely to lead to a breach of the Code. The Panel's ruling of a breach of Clause 15.9 was upheld. The appeal on this point was unsuccessful.

Complaint received **6 November 2001**

Case completed **14 March 2002**

CASE AUTH/1253/11/01

PHARMACIA/DIRECTOR v GLAXOSMITHKLINE and GLAXOSMITHKLINE CONSUMER HEALTHCARE

Promotion of Zyban and NiQuitin CQ

Pharmacia complained about a Zyban (bupropion) leavepiece issued by GlaxoSmithKline and a NiQuitin CQ (nicotine replacement therapy patches) journal advertisement feature issued by GlaxoSmithKline Consumer Healthcare. Pharmacia supplied Nicorette, an alternative nicotine replacement therapy.

As part of the allegations involved an alleged breach of undertaking by GlaxoSmithKline, that aspect was taken up as a complaint by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance given by the Appeal Board.

Pharmacia stated that the claim 'Zyban was shown to be almost twice as effective as a nicotine patch at one year' had been previously ruled to be misleading in breach of the Code because it was not an up-to-date evaluation of all the evidence and did not reflect the evidence clearly (Case AUTH/1085/10/00). The clinical evidence was unchanged and Pharmacia alleged that the minor adaptations to the leavepiece were inadequate and that by failing to comply with the previous ruling GlaxoSmithKline was in breach of Clause 2.

The Panel noted that the previous case, Case AUTH/1085/10/00, concerned the claim 'Clinical trial published in The New England Journal of Medicine. Zyban – shown to be almost twice as effective, in patients motivated to stop, as a nicotine patch at one year'. The Panel had considered that the efficacy of bupropion relative to nicotine replacement therapy was an area of emerging clinical opinion. Particular care should be taken to ensure that the issue was treated in a balanced manner. The page at issue presented some of the results of the only comparative study between Zyban and the nicotine patch in the form of a bar chart. Only the point prevalence abstinence data for the nicotine patch and for Zyban was shown which indicated that Zyban was almost twice as effective as the nicotine patch. The claim above the bar chart stated 'Zyban … almost twice as effective … as a nicotine patch at one year'. The data relating to placebo and Zyban plus the nicotine patch was not shown. If this data had been presented readers would have seen that in the study nicotine patches were no more effective than placebo. Such a result did not represent the balance of evidence with regard to nicotine patches. The weak effect of the nicotine patch according to the point prevalence analysis was commented upon by the study authors. Presentation of all the study data would also have shown that the addition of a nicotine patch to bupropion had no statistically significant additional effect. The Panel considered that whilst the limited amount of data presented were accurate it had not been put into context with the rest of the study data. The Panel questioned whether the comparative efficacy of Zyban vs nicotine patches represented the balance of the evidence given that nicotine patches appeared in this study to be no better than placebo. Insufficient information had been provided. The data was misleading in this regard. A breach of the Code was ruled.

Upon appeal by GlaxoSmithKline in Case AUTH/1085/10/00, the Appeal Board noted that the study design included two placebos, a placebo tablet and a placebo patch. The results in the leaflet were for the nicotine patch plus placebo tablet and Zyban plus placebo patch. Further this was the only study to compare Zyban with a nicotine patch. The Appeal Board was concerned about the abnormally high placebo response such that the study was unable to demonstrate a statistically significant difference between the nicotine patch, a known active, and placebo with regard to point prevalence at 12 months (the primary efficacy measure in the study). The Appeal Board noted that a statistically significant difference had been shown between the nicotine patch and placebo with regard to continuous abstinence at all time points. The Appeal Board noted the authors' view that it was unclear why the nicotine patch produced weak effects according to the point prevalence data and that one study had suggested that the use of two placebos in a control group might produce higher smoking cessation rates than the use of a single placebo. The Appeal Board noted however that the study had been published in a peer reviewed journal and mentioned in the Cochrane Review. The result shown for the nicotine patch was corroborated by other studies.

The Appeal Board noted the overall presentation of the data; the page at issue was headed 'Clinical trial published in The New England Journal of Medicine'. Beneath the graph depicting the Zyban and nicotine patch data the phrase 'Placebo controlled trial' appeared. The Appeal Board considered that a reader would place reliance on this description and would be assured by the reference to a peer reviewed journal. The Appeal Board considered that insufficient detail had been given about the study and its results. Although the limited amount of data presented were accurate it had not been put into context with regard to the rest of the study data. The Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal was unsuccessful.

Turning to the present case, Case AUTH/1253/11/01, the Panel noted that the claim at issue and the presentation of the data was different to that previously considered. The definition of point prevalence was provided together with details of the study methodology and outcome data for Zyban, the nicotine patch and placebo. The Panel considered that the presentation of the data was sufficiently different to that previously considered such that it was not caught by the undertaking given in Case AUTH/1085/10/00. The Panel thus ruled no breach of the Code in that regard.

Details of the study methodology and outcome data for Zyban, the nicotine patch and placebo were provided. The material stated that this was the only clinical trial comparing Zyban with the nicotine patch and was followed by the claim 'Zyban was shown to be almost twice as effective as a nicotine patch at one year'. The Panel considered that this, in conjunction with the immediate visual impression of the graph, was a strong claim and given the caveats expressed by the study authors was misleading and a breach of the Code was ruled.

The remaining allegations concerned GlaxoSmithKline Consumer Healthcare.

The single page journal feature advertisement was headed 'Prescribe NiQuitin CQ for successful quitting' and discussed NiQuitin in relation to its effect upon craving, safety profile, a stop smoking plan and duration of treatment.

Pharmacia drew attention to the claims 'NiQuitin CQ patches have the advantage of offering constant 24 hour nicotine replacement, significantly reducing morning cravings', and '… compared with the Nicorette 16 hour patch, NiQuitin CQ can significantly reduce cravings both in the morning and throughout the day' which were referenced to Shiffman *et al* (2000). An asterisk referred the reader to a postscript which read 'US Clinical Study – materials used identical to UK except in style'.

A bar chart which depicted the results of the Shiffman *et al* study was entitled 'Lower cravings on waking'. An asterisk led the reader to a footnote beneath the bar chart which read 'Study in smokers who smoked with [sic] 30 minutes of waking and who experience morning cravings'. Pharmacia stated that highly dependent smokers, selected because they had morning cravings, did not represent the smoking population as a whole; a general claim based on this trial was misleading. With regard to this aspect of the study the authors noted 'Generalisation of the results to all smokers was not established ...'. In respect of this issue GlaxoSmithKline Consumer Healthcare had used asterisks next to the claims as a result of Pharmacia's concerns. However, Pharmacia believed it was still not clearly explained to the target audience who would be misled without reference to the small print.

The Panel noted that the advertisement discussed NiQuitin in relation to successful quitting in the general smoking population. A reader would assume that the claims at issue related to the general smoking population rather than the subgroup examined in Shiffman *et al* and that was not so. The footnote beneath the bar chart was insufficient to negate this impression. The claims were misleading as alleged and a breach of the Code was ruled in respect of each claim.

A claim 'The NiQuitin CQ patch reaches effective nicotine levels more rapidly and at a higher plasma concentration than the Nicorette patch' was referenced to a study which compared the pharmacokinetic profiles of nicotine replacement patches (Fant *et al* 2000) and was followed by a graph, adapted from the same study, which depicted the plasma nicotine concentration of NiQuitin and Nicorette over 24 hours.

Pharmacia stated that the use of the word 'effective' could not be substantiated by direct head-to-head clinical trial data in terms of 'craving symptoms relief' or more importantly as a measure of efficacy as defined by 'smoking cessation quit rates'. The efficacy of different patches was further reflected in an up-to-date evaluation in the Cochrane Database which stated clearly that wearing the patch for 16 hours (as with Nicorette) was as effective as wearing it for 24 hours (as with NiQuitin CQ).

The Panel noted that Fant *et al* was a pharmacokinetic crossover study to compare the absorption characteristics of 3 transdermal nicotine patches. The study showed that 21mg 24 hour patches delivered a higher relative dose of nicotine over the course of a day than the 15mg 16 hour patch as reflected by higher AUC values. This finding was significant under both acute dosing (0-24hr) and steady state conditions (48-72hr). The authors noted that further study would be required to determine definitively the overall clinical advantages and disadvantages of the differing profiles of nicotine delivery of the various patches. Fant *et al* was not an efficacy study. The claim at issue followed a comparative efficacy discussion and, in the opinion of the Panel implied that the results were of clinical significance ie that the pharmacokinetic profile of NiQuitin CQ would lead to more people being able to successfully quit smoking than with Nicorette. This was not known. The claim was misleading in this regard and a breach of the Code was ruled.

Pharmacia alleged that the claim 'It is the only patch with an advanced rate controlling membrane, ensuring consistent nicotine delivery over 24 hours' was misleading and could not be substantiated. While the different patch systems had differing delivery technology, there was no evidence that one was more advanced than another, especially in relation to clinical outcomes and smoking cessation quit rates. This was again reflected in the Cochrane Database of Systematic Reviews by its recognition that wearing the patch for 16 hours was as effective as wearing it for 24 hours.

The Panel noted that the NiQuitin patch was the only patch available in the UK with an integral rate controlling membrane and GlaxoSmithKline Consumer Healthcare's submission that in its view this represented an advance over previous technologies. The Panel considered that the term 'advanced' implied that the rate controlling membrane was clinically superior to other delivery systems. There was no evidence in this regard. The Panel also noted that The Cochrane Review on Nicotine replacement therapy for smoking cessation 2001 concluded that there 'was no evidence of a difference in clinical effectiveness for 16 hour compared to 24 hour patch'. The Panel considered the claim misleading and not capable of substantiation as alleged and breaches of the Code were ruled.

Pharmacia Limited complained about the promotion of Zyban (bupropion) by GlaxoSmithKline and

NiQuitin CQ (nicotine replacement therapy (NRT) patches) by GlaxoSmithKline Consumer Healthcare. The items at issue were a Zyban leavepiece (ref A42361 20263716-Alp/June 2001) and a NiQuitin CQ journal advertisement feature (ref NCQ/PWT/0901/002). The leavepiece was intended for general practitioners, practice nurses and pharmacists and the advertisement had been run in the GP trade press in September. Pharmacia supplied Nicorette, an alternative nicotine replacement therapy.

As part of the allegations involved an alleged breach of undertaking, that aspect was taken up as a complaint by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance given by the Appeal Board.

1 Zyban leavepiece

Claim 'Zyban was shown to be almost twice as effective as a nicotine patch at one year'

The page at issue was headed 'In the only clinical trial to compare Zyban with a nicotine patch, published in the New England Journal of Medicine' followed by the claim 'Zyban was shown to be almost twice as effective as a nicotine patch at one year'. The claim was referenced to Jorenby *et al* (1999) and appeared above a bar chart which depicted the percentage of patients 'abstinent at one year (point prevalence – defined as % patients abstinent in 7 days prior to end point) [Primary Efficacy Parameter]' as 16.4% for nicotine patch 21mg/day and 30.3% for Zyban 300mg/day. An asterisk adjacent to the Zyban data referred the reader to a footnote which read 'p<0.01 vs placebo and nicotine patch'. Further details about the study appeared in the bottom left-hand corner of the page; '… A high placebo response rate (15.6%) for point prevalence abstinence at one year, resulted in no statistically significant difference from nicotine patch. Continuous abstinence rates at one year: Zyban (18.4%), nicotine patch (9.8%) and placebo (5.6%) where the differences between Zyban and nicotine patch, and both active treatments over placebo were significant (p<0.001)'.

COMPLAINT

Pharmacia stated that in a previous complaint submitted by it, Case AUTH/1085/10/00, the claim had been ruled to be misleading in breach of Clause 7.2 of the Code because it was not an up-to-date evaluation of all the evidence and did not reflect the evidence clearly.

The clinical evidence was unchanged and the minor adaptations to the leavepiece were alleged to be inadequate. By failing to comply with the previous ruling Pharmacia alleged that GlaxoSmithKline was also in breach of Clause 2.

The basic tenet of Pharmacia's original complaint was that the results of the single trial used to support the claim did not represent the evidence base as a whole. This was supported by the most recent evaluation of efficacy – the Cochrane Database of Systematic Reviews 2001. Its review of smoking cessation interventions included the comment that the efficacy of Zyban required further study and consideration. The Cochrane database was used by West *et al* (2000) as a source for developing smoking cessation guidelines for health professionals. In that document he concluded that: 'It is not yet clear whether bupropion is more effective than NRT. One randomised controlled trial has found a higher one year sustained abstinence rate with bupropion than a transdermal patch in the context of a behavioural support package. Further research is needed before any firm conclusion can be drawn.'

Further, there had been in the region of over 100 randomised trials looking at nicotine replacement therapy and efficacy.

When writing to GlaxoSmithKline the Authority asked it to comment about the alleged breach of undertaking in relation to Clause 22 of the Code as well as Clause 2 which had been referred to by Pharmacia.

RESPONSE

GlaxoSmithKline stated that the leavepiece presented the results of the only double-blind, placebo-controlled study to directly compare Zyban with a nicotine patch, published in The New England Journal of Medicine. GlaxoSmithKline had taken great care to ensure that the information was presented in an accurate, balanced and contextual manner. In the previous complaint, Case AUTH/1085/10/00, regarding a similar piece, both the Panel and the Appeal Board had considered that 'although the limited amount of information provided was accurate it had not been put into context with the rest of the study'.

In Case AUTH/1085/10/00 the Panel had also questioned whether the comparative efficacy of Zyban vs nicotine patch represented the balance of evidence, given that nicotine patch appeared in this study to be no better than placebo. GlaxoSmithKline had explained that an unusually high placebo response rate for point prevalence abstinence at 12 months had resulted in no statistical difference from the nicotine patch. However, the 12 month continuous abstinence rates found the nicotine patch to be 1.8-fold more effective than placebo (9.8% vs 5.6%; p<0.001) which fell in the range reported by the Cochrane review of NRT. Moreover, Zyban was found to be twice as effective as the nicotine patch for both the 12 month point prevalence (30.4% vs 16.4%; p<0.001) and continuous abstinence (18.4% vs 9.8%; p<0.001) end points. Having reviewed GlaxoSmithKline's appeal submission, the Appeal Board noted that 'the study had been published in a peer reviewed journal and mentioned in the Cochrane review. The results shown for the nicotine patch were corroborated by other studies'.

Thus, it had been GlaxoSmithKline's firm understanding following the Appeal Board ruling (January 2001) that the claim 'Zyban was shown to be almost twice as effective as a nicotine patch at one year' could be used, providing it was put into context with the rest of the study results. Further information and study details were now provided in the context of presenting results from the Jorenby study. For

comparison, GlaxoSmithKline provided a copy of the original item at issue in Case AUTH/1085/10/00.

Specifically, the 12 month point prevalence rate for the placebo group, and the 12 month continuous abstinence rates for Zyban, nicotine patch and placebo, had been included in the information below the graph. Additionally, GlaxoSmithKline had pointed out that the high placebo point prevalence rate was not significantly different from that for the nicotine patch, but for continuous abstinence both Zyban and nicotine patch were significantly more effective than placebo.

Thus, the data presented in the graph had been carefully put into context with the rest of the study results. GlaxoSmithKline was of the firm opinion that the graph and accompanying information were factual and fair in their reflection of the results for this study. Hence, GlaxoSmithKline did not believe that this item was in breach of Clause 7.2 or Clause 2.

GlaxoSmithKline also believed that it had taken into account the previous Appeal Board Ruling and had honoured its undertaking and was, therefore, not in breach of Clause 22.

PANEL RULING

The Panel noted that the previous case, Case AUTH/1085/10/00, concerned the claim 'Clinical trial published in The New England Journal of Medicine. Zyban – shown to be almost twice as effective, in patients motivated to stop, as a nicotine patch at one year'.

The Panel had considered that the efficacy of bupropion relative to NRT was an area of emerging clinical opinion. Particular care should be taken to ensure that the issue was treated in a balanced manner in promotional material. The page at issue presented some of the results of the only comparative study between Zyban and the nicotine patch in the form of a bar chart. Only the point prevalence abstinence data for the nicotine patch and for Zyban was shown which indicated that Zyban was almost twice as effective as the nicotine patch. The claim above the bar chart stated 'Zyban … almost twice as effective … as a nicotine patch at one year'. The data relating to placebo and Zyban plus the nicotine patch was not shown on the bar chart. If this data had been presented readers would have seen that in the study nicotine patches were no more effective than placebo. Such a result did not represent the balance of evidence with regard to nicotine patches. The weak effect of the nicotine patch according to the point prevalence analysis was commented upon by the study authors. Presentation of all the study data would also have shown that the addition of a nicotine patch to bupropion had no statistically significant additional effect. The Panel considered that whilst the limited amount of data presented were accurate it had not been put into context with all of the rest of the study data. The Panel questioned whether the comparative efficacy of Zyban vs nicotine patches represented the balance of the evidence given that nicotine patches appeared in this study to be no better than placebo. Insufficient information had been provided. The data was misleading in this regard. A breach of Clause 7.2 was ruled.

Upon appeal by GlaxoSmithKline the Appeal Board noted that the study at issue, Jorenby *et al* 1999, had been published in The New England Journal of Medicine. The study design included two placebos, a placebo tablet and a placebo patch. The results in the leaflet were for the nicotine patch plus placebo tablet and Zyban plus placebo patch. The Appeal Board noted that the difference in abstinence rates between the Zyban and nicotine patch groups was statistically significant with regard to both point prevalence and continuous abstinence at 12 months. Further this was the only study to compare Zyban with a nicotine patch.

The Appeal Board noted Glaxo Wellcome's submission about the study design. The Appeal Board was concerned about the abnormally high placebo response such that the study was unable to demonstrate a statistically significant difference between the nicotine patch, a known active, and placebo with regard to point prevalence at 12 months (the primary efficacy measure in the study). The Appeal Board noted that a statistically significant difference had been shown between the nicotine patch and placebo with regard to continuous abstinence at all time points. The Appeal Board noted the authors' view that it was unclear why the nicotine patch produced weak effects according to the point prevalence data and that one study had suggested that the use of two placebos in a control group might produce higher smoking cessation rates than the use of a single placebo. The Appeal Board noted however that the study had been published in a peer reviewed journal and mentioned in the Cochrane Review. The result shown for the nicotine patch was corroborated by other studies.

The Appeal Board noted the overall presentation of the data showing Zyban to be almost twice as effective as a nicotine patch; the page at issue was headed 'Clinical trial published in The New England Journal of Medicine'. Beneath the graph depicting the Zyban and nicotine patch data the phrase 'Placebo controlled trial' appeared. The Appeal Board considered that a reader would place reliance on this description and would be assured by the reference to a peer reviewed journal. The Appeal Board considered that insufficient detail had been given about the study and its results. Although the limited amount of data presented were accurate it had not been put into context with regard to the rest of the study data. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal was unsuccessful.

Turning to the present case, Case AUTH/1253/11/01, the Panel noted that the claim at issue and the presentation of the data was different to that previously considered. The definition of point prevalence was provided together with details of the study methodology and outcome data for Zyban, the nicotine patch and placebo. The Panel considered that the presentation of the data was sufficiently different to that previously considered such that it was not caught by the undertaking given in Case AUTH/1085/10/00. The Panel thus ruled no breach of Clauses 22 and 2 of the Code.

The Panel noted that GlaxoSmithKline had also responded in relation to the requirements of Clause 7.2

of the Code. The Panel noted that the presentation of the data was such that details of the study methodology and outcome data for Zyban, the nicotine patch and placebo were provided. The material stated that this was the only clinical trial comparing Zyban with the nicotine patch and was followed by the claim 'Zyban was shown to be almost twice as effective as a nicotine patch at one year'. The Panel considered that this, in conjunction with the immediate visual impression of the graph, was a strong claim and given the caveats expressed by the study authors was misleading and a breach of Clause 7.2 of the Code was ruled.

2 Journal advertisement feature

The single page advertisement was headed 'Prescribe NiQuitin CQ for successful quitting' and discussed NiQuitin in relation to its effect upon craving, safety profile, a stop smoking plan and duration of treatment.

Pharmacia stated that it had a number of concerns with this piece which was originally developed for use in the consumer domain but was now part of a promotional campaign to general practitioners.

GlaxoSmithKline Consumer Healthcare responded to this part of the complaint.

a) Claims 'NiQuitin CQ patches have the advantage of offering constant 24 hour nicotine replacement, significantly reducing morning cravings', and

'… compared with the Nicorette 16 hour patch, NiQuitin CQ can significantly reduce cravings both in the morning and throughout the day'

Each claim was referenced to Shiffman *et al* (2000) and an asterisk referred the reader to a postscript which read 'US Clinical Study – materials used identical to UK except in style'.

A bar chart which depicted the results of Shiffman *et al* was entitled 'Lower cravings on waking'. An asterisk led the reader to a footnote beneath the bar chart which read 'Study in smokers who smoked with [sic] 30 minutes of waking and who experience morning cravings'.

COMPLAINT

Pharmacia stated that Shiffman *et al* looked at highly dependent smokers selected because they had morning cravings. These smokers did not represent the smoking population as a whole; a general claim based on this trial was misleading and in breach of Clause 7.3. With regard to this aspect of the study the authors noted 'The study has some limitations. The study was conducted on smokers who reported higher craving in the morning and who smoked their first cigarette within the first 30 mins of waking. Generalisation of the results to all smokers was not established ...'.

In respect of this issue GlaxoSmithKline had used asterisks next to the claims as a result of Pharmacia's concerns. However, Pharmacia believed it was still not clearly explained to the target audience who would be misled without reference to the small print.

RESPONSE

GlaxoSmithKline Consumer Healthcare stated that these claims were substantiated by the direct head-to-head clinical study, published in a peer-reviewed journal, demonstrating that the NiQuitin CQ 24 hour patch provided greater relief of morning cravings and cravings all day long than the Nicorette/Nicotrol 15mg 16 hour patch (Shiffman *et al*). For morning cravings, NiQuitin CQ patch demonstrated significantly lower mean craving scores during days 1-3, 4-7 and 8-14 ($p<0.001$). The same was true for mean all-day craving scores (days 1-3 and days 4-7 $p<0.001$; days 8-14, $p=0.003$).

It was true that the population studied in this trial smoked within 30 minutes of waking and experienced higher levels of cravings in the morning than the rest of the day. GlaxoSmithKline Consumer Healthcare accepted that it was appropriate to provide a superscript explaining this qualification on claims based on this study, and had undertaken to do so in future. However, GlaxoSmithKline Consumer Healthcare did not believe this to be a highly relevant limitation of the study validity. Several data sources demonstrated that the majority of smokers experienced more craving in the morning (Shiffman *et al*, 1998) and smoked within 30 minutes of waking (INRA, unpublished results from Boyle *et al* 2000. The European Journal of Public Health gave the study methodology and the spreadsheets provided gave the unpublished results from Boyle). In a representative sample of 609 smokers in the UK, 66.7% reported smoking their first cigarette within 30 minutes of waking.

PANEL RULING

The Panel noted that Shiffman *et al* (2000) examined the relief of craving and withdrawal, particularly in the morning hours of NiQuitin and Nicorette. The 244 participants, all of whom were attempting to quit smoking, had to meet qualifying criteria, *inter alia*, smoke within 30 minutes of waking, report more craving for cigarettes in the morning than the rest of the day and report high motivation and efficacy for quitting. The results demonstrated that 24 hour wear of NiQuitin yielded consistently better relief of craving and withdrawal than Nicorette and also appeared to lead to more abstinence. The authors noted that the study had some limitations; it was conducted on smokers who reported higher craving in the morning and who smoked their first cigarette within 30 minutes of waking. Generalisation of the results to all smokers was not established although the characteristics of the sample matched those for most treatment studies. The analyses included subjects who had smoked at low levels after the quit day. Treatment assignment was not completely blind: active patches were labelled and placebo patches were not matched to the 15mg/16 hour patch.

However, the double dummy design masked treatment assignment by having all subjects wear a patch overnight. The study was limited to two weeks following quitting, the period during which both symptom intensity and relapse risk peak. In that regard the Panel noted that NiQuitin CQ had a ten

week treatment course. The study authors also discussed its methodological strengths and concluded that further studies of differences among nicotine replacement strategies in different populations of smokers might help optimize the effects of nicotine replacement therapy.

The Panel noted that the advertisement discussed NiQuitin in relation to successful quitting in the general smoking population. A reader would assume that the claims at issue related to the general smoking population rather than the subgroup examined in Shiffman *et al* and that was not so. The footnote beneath the bar chart was insufficient to negate this impression. The claims were misleading as alleged and a breach of Clause 7.3 was ruled in respect of each claim.

b) Claim 'The NiQuitin CQ patch reaches effective nicotine levels more rapidly and at a higher plasma concentration than the Nicorette patch'

This claim was referenced to Fant *et al* (2000) a study which compared the pharmacokinetic profiles of nicotine replacement patches and was followed by a graph, adapted from the same study, which depicted the plasma nicotine concentration of NiQuitin and Nicorette over 24 hours.

COMPLAINT

Pharmacia stated that the use of the word 'effective' could not be substantiated by direct head-to-head clinical trial data in terms of 'craving symptoms relief' or more importantly as a measure of efficacy as defined by 'smoking cessation quit rates'. Fant *et al* was a pharmacokinetic study which did not look at efficacy. This was acknowledged by the authors who stated 'Further study will be required to determine definitely the overall clinical advantages and disadvantages of the differing profiles of nicotine delivery of the various patches'.

The efficacy of different patches was further reflected in an up-to-date evaluation in the Cochrane Database which stated clearly that wearing the patch for 16 hours (as with Nicorette) was as effective as wearing it for 24 hours (as with NiQuitin CQ). To mislead in this way was alleged to be in breach of Clause 7.2.

RESPONSE

GlaxoSmithKline Consumer Healthcare stated that a single threshold of effectiveness would be difficult to define for nicotine. However Fant *et al* demonstrated that the lowest levels of nicotine achieved by the NiQuitin CQ 21mg patch (11.8ng/ml) were comparable to the highest level achieved by Nicorette 15mg patch (11.9ng/ml). Thirty minutes after application, the levels achieved by NiQuitin CQ exceeded those ever achieved by Nicorette. Therefore, it could be concluded that either Nicorette never reached effective levels of nicotine, or NiQuitin CQ reached effective levels faster than Nicorette patch.

PANEL RULING

The Panel noted that Fant *et al* was a pharmacokinetic crossover study to compare the absorption characteristics of three transdermal nicotine patches. The study showed that 21mg 24 hour patches delivered a higher relative dose of nicotine over the course of a day than the 15mg 16 hour patch as reflected by higher AUC values. This finding was significant under both acute dosing (0-24hr) and steady state conditions (48-72hr). The authors noted that further study would be required to determine definitively the overall clinical advantages and disadvantages of the differing profiles of nicotine delivery of the various patches.

The Panel noted, as stated by Pharmacia, that Fant *et al* was a pharmacokinetic study not an efficacy study. The claim at issue followed a comparative efficacy discussion and, in the opinion of the Panel, implied that the results were of clinical significance ie that the pharmacokinetic profile of NiQuitin CQ would lead to more people being able to successfully quit smoking than with Nicorette. This was not known. The claim was misleading in this regard and a breach of Clause 7.2 was ruled.

c) Claim 'It is the only patch with an advanced rate controlling membrane, ensuring consistent nicotine delivery over 24 hours'

This claim followed that at issue at point 2b and was referenced to Gorsline *et al* (1992).

COMPLAINT

Pharmacia alleged that this claim of superiority was misleading (Clause 7.2) and could not be substantiated (Clause 7.4).

While Pharmacia acknowledged that the different patch systems had differing delivery technology, there was no evidence that one was more advanced than another, especially in relation to clinical outcomes and smoking cessation quit rates. This was again reflected in the Cochrane Database of Systematic Reviews by its recognition that wearing the patch for 16 hours was as effective as wearing it for 24 hours.

RESPONSE

GlaxoSmithKline Consumer Healthcare stated that the NiQuitin CQ patch was the only patch available that had a rate controlling membrane and, as such, was unique to the UK nicotine replacement therapy market. This was a statement of fact referring to a feature of the product. As such, it was the only patch that contained an integral component to control the rate of nicotine delivery, rather than relying on skin permeability. In that sense, GlaxoSmithKline Consumer Healthcare believed it to be an advance over previous technologies. Indeed GlaxoSmithKline Consumer Healthcare's scientists deliberately set out to develop a patch technology that would enable the pharmacokinetic profile of the NiQuitin CQ patch to be delivered.

Whilst GlaxoSmithKline Consumer Healthcare believed that the NiQuitin CQ patch did indeed represent an advance in technology for the reasons outlined above, it appreciated that the use of the word

'advanced' might, in retrospect, lead to an inference of superiority. Whilst this was not GlaxoSmithKline Consumer Healthcare's intention, it would be willing to remove the word from future materials. However, GlaxoSmithKline Consumer Healthcare believed that the rate controlling membrane, in achieving the pharmacokinetic profile as addressed in point 2b above, was a highly relevant product attribute.

PANEL RULING

The Panel noted that the NiQuitin patch was the only patch available in the UK with an integral rate controlling membrane and GlaxoSmithKline's submission that in its view this represented an advance over previous technologies. The Panel considered that the term 'advanced' implied that the rate controlling membrane was clinically superior to other delivery systems. There was no evidence in this regard. The Panel also noted that The Cochrane Review on Nicotine replacement therapy for smoking cessation 2001 concluded that there 'was no evidence of a difference in clinical effectiveness for 16 hour compared to 24 hour patch'. The Panel considered the claim misleading and not capable of substantiation as alleged. Breaches of Clauses 7.2 and 7.4 were ruled.

Complaint received **16 November 2001**

Case completed **15 February 2002**

CASE AUTH/1254/11/01 *NO BREACH OF THE CODE*

PRIMARY CARE GROUP PRESCRIBING ADVISER v NOVARTIS

Starlix study

A prescribing adviser to a Primary Care Group (PCG) complained on behalf of a practice within the PCG about a study on Starlix (nateglinide) or gliclazide in combination with metformin conducted by Novartis.

The complainant was concerned that the study might influence prescribers to increase prescribing of nateglinide. Although the general practitioner was asked to make the normal prescribing decision and issue an FP10 before identifying patients for inclusion in the study, the ratio of patients to be included was three on nateglinide and metformin to one on gliclazide and metformin. The complainant considered that this ratio was unlikely to represent current prescribing practice.

The Panel noted that the only requirement in the Code relating to post-marketing surveillance studies, clinical assessments and the like was Clause 10.2 which required that they must not be disguised promotion. The study in question was being conducted at a time when Starlix had just been launched. Any study using the product would inevitably have some promotional impact, but studies must not be such that they were promotional *per se*. Studies must be designed to address a valid clinical objective.

The study had a clear objective to quantify, in a naturalistic setting, the expected adverse reactions of hypoglycaemia, serious hypoglycaemia and weight gain which had already been identified in clinical trials. It might also identify previously unrecognised safety issues and provide additional safety information in patients over 75 years of age. Gliclazide had been chosen as the comparator as it was the most frequently used sulphonylurea prescribed in combination for type 2 diabetes in the UK. 6500 patients would be recruited in a proportion of Starlix to gliclazide of approximately 3:1; this would result in an 8 fold increase in the number of patients exposed to Starlix. No more than 40 patients could be recruited at any one centre although it was anticipated that the majority would not recruit more than 10.

The Panel considered that the study was being conducted in an attempt to answer valid scientific questions. Although patients had to be entered into the study on a 3:1 ratio of Starlix to gliclazide, patients would be identified for inclusion only after the decision had been made that they required add-on therapy to metformin. The maximum number of patients that any centre could enter was limited to 40 but not expected to exceed 10. Doctors were required to make their normal prescribing decision, issue a prescription and then identify patients for inclusion.

The Panel considered that the payment of £10 per case record form (CRF) page was reasonable given that the British Medical Association suggested fee for the completion of post-marketing surveillance forms was between £11 and £21.50 per form depending on complexity and the suggested fee for participation in a clinical trial was £148 per hour. There were around 10 CRF pages to complete on behalf of each patient. No other payments would be made.

Overall the Panel did not consider that the study constituted disguised promotion for Starlix. No breach of the Code was ruled on this point. The payments were thus not unacceptable and no breach of the Code was ruled on this point.

A prescribing adviser to a Primary Care Group (PCG) complained about a study on Starlix (nateglinide) or gliclazide in combination with metformin being conducted by Novartis Pharmaceuticals UK Ltd.

The invitation to participate stated that Novartis would like to extend its safety evaluation on nateglinide by comparing its safety in combination with metformin to gliclazide with metformin. Gliclazide had been selected as the comparator as it was the most frequently used sulphonylurea prescribed in combination with metformin for type 2 diabetes. The study would be conducted in accordance with the Guidelines for Safety Assessment of Marketed Medicines (SAMM). Participants would make their normal prescribing decision, issue an FP10 and then identify patients for inclusion. Each participant would enrol up to a maximum of 40 patients in the ratio 3:1 ie three patients to receive nateglinide plus metformin for every one patient receiving gliclazide plus metformin. A payment of £10 per case record form (CRF) page would be paid in accordance with British Medical Association (BMA) rates. It was expected that the number of pages for a patient completing the six month observation period would vary but would be in the order of ten.

COMPLAINT

The complainant stated that a practice in the PCG had forwarded the invitation to her and had expressed concern that the proposed study might be seen to influence prescribers to increase prescribing of nateglinide.

Although the general practitioner was asked to make the normal prescribing decision and issue an FP10 before identifying patients for inclusion in the study, the ratio of patients to be included was 3:1 nateglinide:gliclazide. The complainant considered that it was unlikely that current practice, certainly in her PCG, would be to prescribe a combination of nateglinide and metformin in preference to gliclazide and metformin in three out of four patients and the complainant would therefore echo the concern of the GP practice.

When writing to Novartis, the Authority drew attention to Clauses 10.2 and 18.1 of the Code.

RESPONSE

Novartis emphasised that the study had been designed to extend the safety evaluation of nateglinide in a naturalistic setting; it had not been designed as a promotional activity for the product. The Medicines Control Agency (MCA) reviewed the protocol for the study, together with the letters of invitation, prior to their use.

The study in question was an unblinded (open), observational, non-interventional cohort study. It was intended to collect data from 6500 patients with type 2 diabetes through the involvement of approximately 650 GPs (average of 10 patients per centre). In clinical trials 640 patients were treated with Starlix in combination with metformin, the results of the SAMM study would thus provide an eight fold increase in exposure data in terms of safety profile. Enrolment of patients into the study would take place over a 15 month period, which commenced at the end of October 2001.

Centres contacted to take part in the study had been identified as those known to have a special interest in diabetes, particularly those centres containing general practitioners who ran a dedicated diabetic clinic or who had an interest in or previous experience of SAMM studies.

The complainant's letter suggested that they might have misunderstood the study participation criteria. As the invitation letter explained, the study had been designed in line with the SAMM Guidelines which advocated wherever possible the use of a comparator arm against which the profile of a new medicine could be assessed. In this instance the combination of gliclazide and metformin had been selected as the comparator since it represented the most frequently used sulphonylurea combination currently in use.

In order to compare the nateglinide combination with an appropriate number of gliclazide combination comparator patients a ratio of 3:1 had been selected. The three to one ratio acknowledged that Starlix was a newly introduced product, whilst the comparator was a treatment with a well established safety profile. The unbalanced ratio therefore permitted a more precise estimate of the new product's safety profile. To participants in the study, the ratio meant that for every three nateglinide patients they chose to include in the study they were at liberty to include one on the gliclazide combination. The total number of patients entered into the study for an individual prescriber might not exceed 40 in total on either combination.

Novartis had not in anyway suggested that the 3 to 1 ratio selected for this study would represent the normal distribution of prescribing in an individual GP practice but merely pointed out that doctors choosing to take part in the study might enter patients in that ratio. As the complainant acknowledged, the emphasis was clearly placed on prescribers to enrol patients in the study only after they had made the decision to prescribe the product and issued an FP10.

Novartis did not accept therefore that the arrangements for this study constituted a breach of Clause 10.2 of the Code.

In addition, Novartis confirmed that the level of payment for the completion of CRFs in this study had been selected to comply with BMA recommendations. Participants would be expected to complete around ten pages of information in respect of an individual patient completing the six month observation period of the study. Novartis' view was that a payment of £10 per CRF page in relation to the level of work anticipated was entirely justifiable. Novartis did not accept that these arrangements constituted a breach of Clause 18.1 of the Code.

PANEL RULING

The Panel noted that the MCA had reviewed the protocol for the study, together with the letters of invitation, prior to their use.

The only requirement in the Code relating to post-marketing surveillance studies, clinical assessments and the like was Clause 10.2 which required that they must not be disguised promotion. The study in question was being conducted at a time when Starlix

had just been launched. Any study using the product would inevitably have some promotional impact, but studies must not be such that they were promotional *per se*. Studies must be designed to address a valid clinical objective.

The Panel noted that the study had a clear objective to quantify, in a naturalistic setting, the expected adverse reactions of hypoglycaemia, serious hypoglycaemia and weight gain which had already been identified in clinical trials. In addition the study might also identify previously unrecognised safety issues and might provide additional safety information in patients over 75 years of age. Gliclazide had been chosen as the comparator as it was the most frequently used sulphonylurea prescribed in combination for type 2 diabetes in the UK. The study had been designed such that 6500 patients would be recruited in a proportion of Starlix to gliclazide of approximately 3:1; this would result in an 8 fold increase in the number of patients exposed to Starlix. The maximum number of patients that could be recruited at any one centre was limited to 40 although it was anticipated that the majority of centres would recruit no more than 10.

The Panel considered that the study was being conducted in an attempt to answer valid scientific questions. Although patients had to be entered into the study on a 3:1 ratio of Starlix to gliclazide patients would be identified for inclusion only after the decision had been made that they required add-on therapy to metformin in the management of their diabetes. The maximum number of patients that any centre could enter was limited to 40 but not expected to exceed 10. Doctors were required to make their normal prescribing decision, issue a prescription and then identify patients for inclusion.

The Panel considered that the payment of £10 per CRF page was reasonable given that the BMA suggested fee for the completion of post-marketing surveillance forms was between £11 and £21.50 per form depending on complexity and the suggested fee for participation in a clinical trial was £148 per hour (ref Medeconomics December 2001). There were around 10 CRF pages to complete on behalf of each patient. No other payments would be made.

Overall the Panel did not consider that the study constituted disguised promotion for Starlix. No breach of Clause 10.2 of the Code was ruled. As the study was not disguised promotion it thus followed that there could be no breach of Clause 18.1 of the Code with regard to the payments. The Panel therefore ruled no breach of Clause 18.1.

Complaint received **21 November 2001**

Case completed **8 February 2002**

CASE AUTH/1257/11/01

PFIZER v BAYER

Promotion of Adalat LA

Pfizer complained about an Adalat LA (nifedipine) mailer and leavepiece issued by Bayer. Pfizer marketed Istin (amlodipine).

Pfizer alleged that the claim in the mailer 'Adalat LA has been proven to reduce morbidity and mortality … amlodipine has not' was inaccurate, misleading, exaggerated and disparaging. Data from the PREVENT study and the CAPARES study showed that amlodipine reduced cardiovascular morbidity and mortality. In intercompany correspondence Bayer had stated that the claim related only to hypertensive patients, but this had not been made clear; the claim appeared to apply to all patient groups.

The Panel noted that there was no title or such like on the mailer to state that claims within related to hypertension. Although the page in question stated that the INSIGHT study had confirmed that '… Adalat LA reduces the risk of CV events by up to 47% in hypertensive patients' this was in a small type size and the layout of the page was such that readers would immediately see the claim in question; the qualifying statement regarding hypertension would be missed by many. In the Panel's view readers would interpret the claim as a general statement and assume that it meant that amlodipine had not been shown to reduce either morbidity or mortality in any patient group which was not so. The INSIGHT study had confirmed that nifedipine once daily and co-amilozide were equally effective in preventing overall cardiovascular and cerebrovascular complications of hypertension. Co-amilozide had previously been shown in a placebo-controlled study to reduce cardiovascular events in older hypertensives (MRC-II study). By implication Adalat must also reduce cardiovascular events compared to placebo. The Panel noted that it was no longer ethical to conduct placebo-controlled outcome studies in hypertensive patients. Nonetheless the Panel considered that the claim was misleading and disparaged amlodipine; breaches of the Code were ruled.

The claim 'Adalat LA is the only dihydropyridine calcium antagonist proven to reduce morbidity and mortality in a comparative double-blind trial' appeared in the mailer on the same page as the claim at issue above. The claim 'Adalat LA is the only dihydropyridine supported by outcome data from a comparative double-blind study' appeared in the leavepiece on a page which discussed the risks of hypertension in relation to cardio and cerebrovascular morbidity and mortality. Pfizer alleged that the claims were misleading, all-embracing and disparaging. Amlodipine and nitrendipine were dihydropyridines and both had been shown in double-blind placebo-controlled trials to reduce morbidity and mortality. In intercompany discussions Bayer had defined 'comparative' as meaning compared to another medicine and did not consider placebo as comparative; the company had also discounted the nitrendipine trials because the product had no UK licence.

On balance the Panel considered that it was not unreasonable to disregard nitrendipine when making promotional claims to UK health professionals. The Panel considered that the claims would be read as comparisons between Adalat LA and another medicine. The amlodipine placebo-controlled data did not fit this description on this narrow basis. The Panel thus did not consider the claim exaggerated and no breach of the Code was ruled.

The Panel considered that the claims, which related to the INSIGHT study, gave the impression that Adalat LA had been shown to reduce morbidity and mortality more than an active comparator. This was not the case. The Panel noted its comments above about the relationship between the outcomes of the INSIGHT and the MRC-II studies and considered that the basis for the claims had not been adequately explained. The claims were misleading and a breach of the Code was ruled.

With regard to the context in which the claims were made, the relevant page in the leavepiece referred to hypertension. The Panel considered that it was reasonable to assume the claim also related to hypertension. No breach of the Code was ruled. With regard to the mailing, the Panel noted its comments above and considered that it was not clear that the claim related to hypertension and ruled a breach of the Code.

The claim 'Unlike amlodipine, Adalat LA does not increase heart rate' appeared in the mailer. A table of comparative data in the leavepiece had a tick for Adalat LA and a cross for amlodipine next to the statement 'No change in heart rate'. A similar table on the next page had a tick for Adalat LA and a question mark for generic nifedipine adjacent to the claim 'For no change in heart rate'. Pfizer alleged that these claims were misleading and disparaged amlodipine. The Adalat LA summary of product characteristics (SPC) referred to tachycardia. In addition there was evidence from a 24 hour ambulatory blood pressure monitoring study that amlodipine did not increase heart rate. The Istin SPC clearly supported this; it also referred to the possibility of, *inter alia*, ventricular tachycardia with calcium channel blockers generally, but that these rhythm disturbances were rarely reported and could not be distinguished from the natural history of the underlying disease. Pfizer alleged that the claims were inconsistent with the respective SPCs.

The Panel noted that there was a difference between the occurrence of tachycardia as a side-effect and an overall general increase in heart rate which occurred due to the pharmacodynamic properties of a medicine. According to their SPCs both Adalat LA and Istin might precipitate tachycardia in some patients. Each medicine had more influence on blood vessels than on the heart muscle. Although studies had shown that the administration of amlodipine resulted in a sustained rise in norepinephrine levels, suggesting an increase in sympathetic activation, the clinical significance of the results was unknown (de Champlain *et al*).

The Panel considered that the claim 'Unlike amlodipine, Adalat LA does not increase the heart rate' was misleading and disparaging as alleged. It was unclear whether the increase in heart rate related to a side effect or to the pharmacodynamic properties of the medicines. The clinical relevance of the de Champlain data was unknown. Breaches of the Code were ruled. The Panel did not consider that the claim promoted Adalat LA in a way that was inconsistent with its SPC. No breach of the Code was ruled in that regard. The Panel considered that the table in the leavepiece comparing Adalat LA with amlodipine was covered by these rulings. The other table in the leavepiece compared Adalat LA with generic nifedipine. As above the Panel considered that it was unclear as to whether an increase in heart rate related to an adverse event or the pharmacodynamic properties of Adalat LA. A breach of the Code was ruled. As above the Panel did not consider that the claim promoted Adalat LA in a way which was inconsistent with its SPC. The table did not refer to amlodipine and so there could be no disparagement of that product. No breaches of the Code were ruled.

Pfizer Limited complained about a mailer (unreferenced) and a leavepiece (ref OVADL 572) for Adalat LA (nifedipine) issued by Bayer plc, Pharmaceutical Division. Pfizer marketed Istin (amlodipine).

Bayer stated that neither the mailer nor the leavepiece were still in use; the mailer was sent in May 2001 to target doctors, hospital doctors and hospital pharmacists. The leavepiece was available until 11 April for the sales force as a third line detail leavepiece.

1 Claim 'Adalat LA has been proven to reduce morbidity and mortality … amlodipine has not'

This headline claim appeared in the mailer referenced to Brown *et al* (2000) and was followed by the claim 'The positive results of the INSIGHT Study confirm that Adalat LA reduces the rate of CV events by up to 47% in hypertensive patients'. 'Adalat LA is the only dihydropyridine calcium antagonist proven to reduce morbidity and mortality in a comparative double-blind trial' appeared in a highlighted box at the bottom of the page.

COMPLAINT

Pfizer considered that the claim was inaccurate, misleading, exaggerated and disparaged amlodipine. Pfizer alleged breaches of Clauses 7.2 and 8.1 of the Code for the following reasons.

Pfizer noted that amlodipine had been shown to reduce cardiovascular morbidity and mortality in several clinical studies. For example PREVENT (Pitt *et al*, 2000) was a three year, multicentre, randomised, placebo-controlled, double-blind clinical trial of 825 patients with angiographically confirmed coronary artery disease. The study demonstrated that amlodipine reduced the rate of unstable angina (RR 0.67, p=0.01) and the need for coronary revascularisation procedures (RR 0.57, p=0.001). In addition, amlodipine showed significant regression of carotid intima media thickness (IMT) compared to the placebo group.

The CAPARES study (Jørgensen *et al* 2000) was also a multicentre, randomised placebo-controlled, double-blind clinical trial of 625 patients, comparing amlodipine treatment with placebo in patients suitable for elective balloon angioplasty. There were no statistically significant differences in the baseline variables between the treatment groups. The study showed that when amlodipine was given to patients prior to percutaneous transluminal coronary angioplasty (PTCA), there was a significant risk reduction (RR 0.65, p=0.049) in the composite major adverse clinical events as compared to the placebo arm. Clinical events included all-cause mortality, myocardial infarction (MI), coronary artery bypass graft (CABG) and repeat PTCA.

In intercompany correspondence Bayer had stated that the claim related only to hypertensive patients, but this was not clear in its promotional material. Its claim was a generalisation of all population groups with no reference in the claim specific to hypertension.

Amlodipine had been shown to reduce morbidity and mortality whereas the evidence for Bayer's claim was less convincing. Bayer had quoted INSIGHT (Brown *et al*) which compared Adalat LA with co-amilozide in hypertensive patients. The primary endpoint was a composite of cardiovascular and cerebrovascular events, which was in fact numerically greater in the Adalat LA group (6.3% vs 5.8% in co-amilozide group; not statistically significant). When the composite outcomes were separated down, the only significant observations seen between the two groups was a higher incidence of fatal MI (p=0.017) and non-fatal heart failure (p=0.028) which was apparent in the Adalat LA treated group, although the incidence rates of these events were low. The study revealed no benefit of Adalat LA on outcomes and therefore Pfizer did not feel it was appropriate to say that Adalat LA '… has been proven to reduce morbidity and mortality …'. There was no placebo arm to make comparisons with which to support its claim of proven benefit in reducing morbidity and mortality.

RESPONSE

Bayer noted that Pfizer's contention was that it was not clear from the mailer that the claim related only to hypertensive patients; however, the sentence immediately following the claim stated: 'The positive results of the INSIGHT study confirm that Adalat LA reduces the rate of CV events by up to 47% in hypertensive patients'. It was clear that this claim was in relation to hypertensive patients, a licensed indication for Adalat LA; Bayer disagreed with Pfizer's view that the claim was a generalisation of all population groups with no reference in the claim specific to hypertension.

In addition, the following statement, that appeared on the opposite (right hand) page, further highlighted that the mailer promoted Adalat LA only in the context of hypertension.

'The evidence points to Adalat LA:

- Proven to reduce morbidity and mortality in hypertension
- Proven BP lowering efficacy to treatment targets
- Flexible dosing range with low dose option
- Costs less than amlodipine
- Unlike amlodipine, Adalat LA does not increase the heart rate.'

It was clear which patient population this piece referred to by the first two bullet points above that made specific reference to hypertension and blood pressure lowering. Additionally, there was a statement on the reverse side of the mailer which described Adalat LA20 as an 'Ideal starting dose for hypertension'. Therefore it was evident that the mailer related to the use of Adalat LA for the treatment of hypertension and in this context the claim that 'Adalat LA has been shown to reduce morbidity and mortality … amlodipine has not' was true.

Pfizer cited the PREVENT and CAPARES studies to support its claim that amlodipine had been shown to reduce cardiovascular morbidity and mortality. Bayer highlighted some issues in relation to these two studies.

The PREVENT study was performed to assess the angiographic changes in coronary arteries in 825 patients over a 36 month period. The study was not powered to detect morbidity and mortality outcome as per INSIGHT. The primary endpoint was whether amlodipine would reduce the progression of early atherosclerotic segments. The lack of statistical power was highlighted by the study authors who stated '… the statistical power for the detection of a treatment difference in mortality and major morbidity rates was low because of the relatively low incidence rates'. Furthermore, in their discussion, the authors stated 'amlodipine had no effect on the risk of all-cause mortality or major cardiovascular events'.

The PREVENT study did not demonstrate a reduction in cardiovascular events in hypertensive patients and therefore was not comparable to the INSIGHT study. In fact one of the eligibility criteria for this study was a diastolic blood pressure <95mmHg, implying that the patients were either borderline hypertensives or normotensive.

The CAPARES trial assessed the efficacy of amlodipine in reducing restenosis rates and clinical outcomes in 451 patients with stable angina undergoing routine PTCA. Clearly this was a very different patient population to that studied in INSIGHT, which included a much larger number of high-risk hypertensives. This trial was fundamentally different from the INSIGHT study, as it was designed to assess the effect of amlodipine on cardiovascular outcomes in patients undergoing elective angioplasty, rather than in hypertensive patients.

Neither of these two studies investigated the effect of amlodipine on cardiovascular outcomes in hypertensive patients and so they were not comparable to the INSIGHT study. Bayer maintained that amlodipine was not supported by specific morbidity and mortality data in a hypertensive patient population and therefore differed significantly from Adalat LA in this regard. Hence Bayer did not consider that its claim to this effect was in breach of Clause 7.2 of the Code.

Furthermore, as amlodipine did not have a specific indication for use in the patient populations studied in PREVENT and CAPARES, these studies were not relevant to the current discussion.

The design of the INSIGHT study published in The Lancet, a highly respected peer reviewed journal, was robust in that it was a randomised, double-blind, active comparator study conducted on an international scale. The patient numbers involved (n=6321) provided evidence that this was a landmark trial unlike the PREVENT and CAPARES studies which involved only hundreds of patients.

The use of a composite endpoint was very common in outcome studies and the statistical analysis accounted for this design. The fact that cardiovascular and cerebrovascular events were numerically greater in the Adalat LA group was irrelevant, as this difference was not statistically significant. Slight numerical differences in event rates were not uncommon in studies of this size.

In the design of outcome studies, composite endpoints were invariably studied in order to ensure that the required number of events needed to demonstrate a statistically significant difference between treatment groups was reached. At the same time, the number of patients that needed to be studied to achieve this was minimised. For this reason many recently conducted outcome trials had utilised this design, including some Pfizer-sponsored studies, such as CAPARES, PRAISE (Packer *et al*, 1996) and ALLHAT (Davies *et al*, 1996). The study of individual endpoints in this context was often of little use as the absolute frequency of these events was so low that small differences could be misleading. This was clearly the case for the INSIGHT study with regard to the individual endpoints of fatal MI (n=21) and non-fatal heart failure (n=35).

The objective of INSIGHT was to demonstrate non-inferiority between Adalat LA and co-amilozide, which had previously been shown to reduce cardiovascular events in hypertensive patients in the Medical Research Council Trial of Treatment of Hypertension in Older Adults (1992) MRC-II study. Therefore, it was not surprising that the study revealed no benefit of Adalat LA on outcomes as noted by Pfizer.

Combining the fact that the MRC-II study demonstrated a significant reduction in events in a hypertensive population, and the similar event rates in the Adalat LA and co-amilozide treatment groups in INSIGHT, showed that Adalat LA was similar to co-amilozide with respect to event reduction in this patient population.

INSIGHT discussed this point in detail and put these results into context by demonstrating the expected event rate in this patient population (based on Framingham equation using baseline risk) had they been left untreated for the duration of the study.

When this event rate was compared with the observed event rate in the Adalat LA treatment arm, it was apparent that Adalat LA reduced events by a significant 47%. This was a very dramatic reduction and justified the claim that 'Adalat LA has been proven to reduce morbidity and mortality'.

Numerous placebo-controlled trials had been completed since the 1970s demonstrating the beneficial effects of primarily diuretics and beta-blockers, including MRC-I, MRC-II, SHEP (1991) and Amery *et al* (1985) (EWPHE) which demonstrated beyond any doubt that reducing blood pressure with these agents was beneficial and consequently it was deemed unethical to compare Adalat LA with placebo in the INSIGHT study. Other studies in recent years had also employed similar design, such as STOP-2 (Hansson *et al*, 1999), due to the ethical issues surrounding the use of placebos in hypertension studies. This explained the statement by Pfizer that 'There was no placebo arm to make comparisons with to support its claim of proven benefit in reducing morbidity and mortality'.

Therefore, Bayer disagreed that its mailer was inaccurate, misleading and disparaging to amlodipine and consequently it maintained that it was not in breach of Clauses 7.2 and 8.1 of the Code.

PANEL RULING

The Panel noted that according to its SPC Adalat LA (20, 30 and 60mg) was indicated for the 'treatment of mild to moderate hypertension. For the prophylaxis of chronic stable angina pectoris either as monotherapy or in combination with a beta-blocker'. According to the Istin SPC it was indicated in 'hypertension, prophylaxis of chronic stable angina pectoris; Prinzmetals (variant) angina when diagnosed by a cardiologist. In hypertensive patients amlodipine has been used in combination with a thiazide diuretic, alpha-blocker, beta-andrenoceptor blocking agent, or an angiotensin converting enzyme inhibitor. For angina, Istin may be used as monotherapy or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta-blockers. Amlodipine is well tolerated in patients with heart failure and a history of hypertension or ischaemic heart disease'.

The Panel noted that there was no title or such like on the mailing to state that the claims within related to hypertension. The layout of the page at issue was such that readers would immediately see the claim 'Adalat LA had been proven to reduce morbidity and mortality… amlodipine has not' and the highlighted box of text which read 'Adalat LA is the only dihydropyridine calcium antagonism proven to reduce morbidity and mortality in a comparative double-blind trial'. Between the claim and the box of text, in a small type size, was the statement 'The positive results of the INSIGHT Study confirm that Adalat LA reduces the rate of CV events by up to 47% in hypertensive patients'. The Panel did not consider that it was clear that the claim related to the treatment of hypertension. The qualifying statement would be missed by many readers. In the Panel's view readers would interpret the claim as a general statement and assume that it meant that amlodipine had not been shown to reduce either morbidity or mortality in any patient group which was not so as shown by the results of PREVENT and CAPARES. The Panel noted that the significant reduction in the composite major adverse clinical events shown for amlodipine in the CAPRES study, which included all cause mortality, was driven mainly by the reduction in the need for repeat PTCA. There was no significant reduction in the incidence of death. The Panel also noted in PREVENT that amlodipine had no effect on the risk of all cause mortality. With regard to the data for Adalat LA in hypertension, the Panel noted that the INSIGHT study showed that nifedipine once daily and co-amilozide were equally effective in preventing overall cardiovascular or cerebrovascular complications. Co-amilozide had previously been shown in a placebo controlled study to reduce cardiovascular events in older hypertensives (MRC-II study). By implication Adalat must also reduce cardiovascular events compared to placebo. The Panel noted that it was no longer ethical to conduct placebo controlled outcome studies in hypertensive patients. Nonetheless the Panel considered that the claim was misleading and that it disparaged amlodipine as alleged. Breaches of Clauses 7.2 and 8.1 were ruled.

2 Claim 'Adalat LA is the only dihydropyridine calcium antagonist proven to reduce morbidity and mortality in a comparative double-blind trial'

This claim appeared in the mailer on the same page as the claim at issue at point 1 in a highlighted box at the bottom of the page.

Claim 'Adalat LA is the only dihydropyridine supported by outcome data from a comparative double-blind study'

This claim was referenced to Brown *et al* (2000) and appeared in the leavepiece on page 2 which discussed the risks of hypertension in relation to cardio and cerebrovascular morbidity and mortality.

COMPLAINT

Pfizer alleged that this claim was misleading, all-embracing and disparaged amlodipine. Pfizer alleged breaches of Clauses 7.2 and 7.10 of the Code.

Pfizer noted that both amlodipine and nitrendipine were dihydropyridine calcium antagonists that had been shown by double-blind placebo-controlled trials to reduce morbidity and mortality. As shown at point 1 above (PREVENT and CAPARES) amlodipine had been shown to reduce morbidity and mortality.

Nitrendipine had been studied in two large clinical trials (Syst-Eur and Syst-China). Syst-Eur was a large multicentre, randomised, placebo-controlled, double-blind trial of 4695 hypertensive patients. Nitrendipine was compared to placebo and demonstrated a significant reduction in major cardiovascular events. This translated to a 5-year absolute benefit of preventing 29 strokes or 53 major cardiovascular events with nitrendipine as compared to placebo.

Syst-China was a large (2394 patients) randomised, placebo-controlled, double-blind study which compared nitrendipine with placebo in Chinese patients with isolated systolic hypertension. This study showed clear benefit for nitrendipine in reducing total mortality (RR 0.39, p=0.003), cardiovascular mortality (RR 0.39, p=0.03) and stroke mortality (RR 0.58, p=0.02). Therefore, both amlodipine and nitrendipine had supporting clinical trial evidence to contradict Bayer's claim that Adalat LA was the only dihydropyridine with proven morbidity and mortality benefit.

In its response to Pfizer, Bayer defined 'comparative' as meaning comparing to another medicine, and did not consider placebo as comparative. Pfizer believed that comparing to placebo was comparative and relevant, with huge clinical importance. Furthermore, Bayer discounted the nitrendipine trials because nitrendipine had no licence in the UK. The two nitrendipine trials mentioned were large well conducted trials that were frequently quoted by key opinion leaders in the UK as strong evidence for managing hypertensive patients, especially those with 'isolated systolic hypertension'. This was further supported by the referencing of both these nitrendipine trials in the British Hypertension Society (BHS) guidelines, as compelling evidence for the use of dihydropyridine calcium antagonists in the management of isolated systolic hypertension. Therefore, Pfizer believed these trials should not be ignored.

Adalat LA was, therefore, not the only dihydropyridine calcium antagonist proven to reduce morbidity and mortality in a comparative double-blind trial. Both amlodipine and nitrendipine had trial evidence that showed they reduced morbidity and mortality.

RESPONSE

Bayer noted that Pfizer cited the PREVENT and CAPARES studies again. Bayer reiterated its comments made in point 1 above with regard to these studies, especially in relation to the patient populations involved. Furthermore, it was clear that the claims made throughout this leavepiece referred to hypertensive patients as on page 2 the title posed the question:

'Does the calcium antagonist you prescribe reduce the risks of hypertension?'

Therefore, it was true that amlodipine was not supported by outcome data in the hypertensive patient population.

The Syst-Eur and Syst-China studies demonstrated reductions in cardiovascular events in hypertensive patients treated with nitrendipine. However, nitrendipine was not available in the UK and therefore its acknowledgement in the piece would not be of relevance to UK prescribers. In addition it could potentially confuse physicians, particularly in light of the similarity in names of the two products (nifedipine and nitrendipine).

Bayer acknowledged that current guidelines made reference to nitrendipine, but this was common practice in all therapy areas where global data was assessed. For example, studies of lovastatin (not licensed in the UK) were mentioned in cholesterol lowering guidelines but not included in the promotional materials of the statin manufacturers. Bayer was not suggesting that these trials be ignored, but that their relevance to the average UK physician was doubtful. Furthermore it was not common practice for companies to include references to products that were not available in the UK in their promotional materials.

In response to the issue concerning the use of the word 'comparative', it was widely accepted amongst the medical community that this word, when used in the context of describing a study, indicated that the comparator was an active medicine rather than placebo. It was usual to describe studies that incorporated a comparison with placebo as 'placebo-controlled' and not 'comparative with placebo'. Therefore the word 'comparative' in this context could only mean a comparison with an active medicine rather than placebo. Bayer agreed that comparing to placebo was relevant and of clinical importance but repeated that placebo-controlled studies in hypertension were no longer deemed to be ethical. The majority of prescribers were aware of this ethical issue and would therefore interpret 'comparative' as indicating that an active medicine was included in this study.

Consequently, Bayer maintained that Adalat LA was the only dihydropyridine calcium antagonist proven to reduce morbidity and mortality in a comparative double-blind trial. Therefore, this claim was neither all-embracing, highly misleading nor disparaging to amlodipine and therefore not in breach of Clauses 7.2 and 7.10 of the Code.

Bayer noted that following the original complaint by Pfizer in May, it had subsequently altered the materials of its next campaign to make it even more explicit that all claims for Adalat LA were in the context of hypertensive patients.

PANEL RULING

The Panel noted Pfizer's submission in relation to nitrendipine and two placebo-controlled studies Syst-Eur and Syst-China. The Panel further noted that nitrendipine was not available in the UK. On balance the Panel considered that it was not unreasonable to disregard nitrendipine when making promotional claims to UK health professionals. It would have been helpful if the position had been made clear. With regard to Pfizer's comments about the placebo-controlled amlodipine data, the Panel considered that the claims would be read as comparisons between Adalat LA and another treatment. The amlodipine data did not fit this description on this narrow basis. The Panel thus did not consider the claim exaggerated as alleged. No breach of Clause 7.10 was ruled.

The Panel considered that both claims gave the impression that Adalat LA had been shown to reduce morbidity and mortality more than an active comparator. This was not the case. The claims related to the INSIGHT study in which nifedipine and co-amilozide had been shown to be equally effective. The Panel noted its comments in point 1 above with

regard to the relationship between the outcome of the MRC-II study and the INSIGHT study and considered that the basis for the claim had not been adequately explained. The claim was misleading and a breach of Clause 7.2 was ruled.

With regard to the context in which the claims were made the Panel noted that the relevant page of the leavepiece was headed 'Does the calcium antagonist you prescribe reduce the risks of hypertension?'. The Panel considered that it was reasonable to assume that all claims on the page thus related to the use of Adalat LA in hypertension. No breach of Clause 7.2 was ruled. With regard to the mailing, the Panel noted its comments in point 1 above and considered that it was not clear that the claim related to hypertension. The Panel ruled a breach of Clause 7.2.

3 Claim 'Unlike amlodipine, Adalat LA does not increase the heart rate'

This claim appeared in the mailer beneath the heading 'The evidence points to Adalat LA'.

A comparative table on page 3 of the leavepiece featured, adjacent to the claim 'No change in heart rate', a tick for Adalat LA and a cross for amlodipine. A similar table on page 4 featured a tick for Adalat LA and a question mark for generic nifedipine once daily adjacent to the claim 'For no change in heart rate'.

COMPLAINT

Pfizer noted that the Adalat LA SPC clearly stated in section 4.8 (undesirable effects) that 'headache, flushing, tachycardia and palpitations may occur …'. Bayer's claim was therefore a complete contradiction of its own SPC. Pfizer considered that contradictions of this manner would not only potentially confuse but also mislead doctors in their understanding of the adverse events of Adalat LA.

There was good evidence that amlodipine did not increase heart rate. Bignotti *et al (1995)* evaluated hypertensive patients on amlodipine and carried out 24 hour ambulatory blood pressure monitoring and heart rate measurements. This study showed good antihypertensive effect without changes in heart rate. The Istin SPC (Section 4.8) clearly supported this. The same section of the SPC also acknowledged the possibility of arrhythmias (including ventricular tachycardia and atrial fibrillation) with calcium channel blockers generally, but that these rhythm disturbances were rarely reported and could not be distinguished from the natural history of the underlying disease.

In Bayer's response to Pfizer, it quoted tachycardia as 'three or more ventricular beats occurring at a rate of 120 beats per minute or more'. However, tachycardia was defined by many cardiology textbooks as a heart rate exceeding 100 beats/min. Therefore, any medicine that induced tachycardia must by definition increase the heart rate. As the Adalat LA SPC had tachycardia as a potential adverse event, then it must also increase heart rate, which contradicted Bayer's claim.

Bayer quoted two clinical papers to help substantiate its claim. The first one (de Champlain *et al*, 1998) compared Adalat LA with amlodipine and evaluated heart rate by palpating the wrist pulse over 30 seconds at specified time points over a period of at least 13 hours. An increase in heart rate with amlodipine was observed for only very brief periods in the study (between hours 4 to 5, and hours 12 to 13). Any increase in heart rate was not sustained and the methodology used in the study raised questions as to the reliability of these findings. In this study heart rate was measured by palpating the radial artery over 30 seconds. This was open to greater human error than 24 hour ambulatory heart rate measurements as in the Bignotti study described above, which showed amlodipine did not affect heart rate. The second paper compared heart rate with placebo, amlodipine and Adalat LA, and demonstrated no variations on heart rate by all three groups (de Champlain *et al* 2000).

Pfizer alleged that Bayer's claims were not only misleading but also disparaging of amlodipine, and therefore breached Clauses 7.2 and 7.10 of the Code. More importantly, such practice in contradicting the two products' SPCs indicated a breach of Clause 3.2 for promoting outside Bayer's licence in terms of being inconsistent with the particulars listed in the respective SPCs.

RESPONSE

Bayer agreed that tachycardia, a clinical entity, had been defined in some textbooks as >100 beats per minute. However, the issue in question Bayer believed was somewhat different.

An 'increase in the heart rate' as stated in the mailer did not refer to the same phenomenon. It was widely thought that small but sustained increases in sympathetic activity leading to small but sustained increases in basal ventricular rate were factors contributing to an increased risk for coronary heart disease. This was clearly very different from tachycardia which was more of an acute phenomenon and unlikely to be sustained. Tachycardia occurred at an incidence of ≥ 0.1% and <1.0% with Adalat LA. The reference to 'tachycardia' in the adverse events section of the Adalat LA SPC was in relation to the acute phenomenon and therefore different from the sustained increases in heart rate that were thought to increase the risk of CHD.

Therefore, Bayer disagreed that this claim was misleading. In Pfizer's original correspondence with Bayer, Pfizer claimed that 'amlodipine does not increase heart rate which is stated clearly in the Istin SPC'. However, in section 4.8 of the SPC, it stated that 'As with other calcium channel blockers the following adverse events have been rarely reported and cannot be distinguished from the natural history of the underlying disease: myocardial infarction arrhythmia (including ventricular tachycardia and atrial fibrillation) and chest pain'. Bayer suggested that this explanation also applied to the statement regarding tachycardia in the Adalat LA SPC.

Bayer highlighted that the studies by de Champlain (1998, 2000) were designed specifically to assess the

effects of nifedipine and amlodipine on circulating catecholamine levels in patients with essential hypertension. The first of these studies demonstrated that Adalat LA did not increase sympathetic activity or heart rate unlike amlodipine. The author stated that 'a significant increase in heart rate was observed with amlodipine after chronic treatment' which corresponded to an increase from 75+/–2 beats per minute to 81+/-2.3 beats per minute in the acute phase. The discussion of these findings stated 'In contrast to observations with the two nifedipine formulations, the chronic treatment with amlodipine was associated with marked and sustained increases by more than 50% in plasma norepinephrine levels in all the 24 hour blood samples taken during the 13 hour period after dose, suggesting that chronic sympathetic activation occurred'.

The fact that the increase in norepinephrine levels occurred in all patients was compelling. On the basis of the results of this study Bayer made the claim in question.

A further study by the same author, although not showing a difference between nifedipine GITS and amlodipine with respect to heart rate, confirmed the findings of the previous study in terms of effects on sympathetic activation.

Additionally the INSIGHT study showed very clearly that there was no increase in heart rate either in the diuretic or Adalat LA group over the duration of the study. Many other studies with Adalat LA supported this observation.

Hence the claim in question was neither misleading nor disparaging of amlodipine and did not breach Clauses 7.2 and 7.10 of the Code. Bayer also maintained that the claim did not constitute promotion outside of the terms of the licence for Adalat LA and therefore was not in breach of Clause 3.2 of the Code.

PANEL RULING

The Panel noted that Section 4.8 of the Adalat LA SPC listed tachycardia as an uncommon (>0.1% <1%) undesirable effect. Section 4.8 of the Istin SPC listed 'arrhythmia (including ventricular tachycardia and atrial fibrillation)' as an adverse event which, as with other calcium channel blockers had been rarely reported and could not be distinguished from the natural history of the underlying disease.

The Panel noted Bayer's submission about the differences between tachycardia, an acute phenomenon, and an increase in heart rate. The Panel further noted the parties' submissions regarding Champlain *et al* (1998 and 2000) and Bignotti *et al*.

Section 5.1 of the SPC described the pharmacodynamic properties of Adalat LA and Istin. Adalat LA was described as a dihydropyridine calcium antagonist with mainly vascular effects. Its main action was to relax smooth muscle both in the coronary and peripheral circulation. Istin was described in similar terms. With respect to its action in reducing total ischaemic burden the Istin SPC stated that total peripheral resistance was reduced but that heart rate remained stable.

The Panel accepted that there was a difference between the occurrence of tachycardia as a side-effect and an overall general increase in heart rate which occurred due to the pharmacodynamic properties of a medicine. According to the SPCs both Adalat LA and Istin might precipitate tachycardia in some patients as an adverse event. According to the pharmacodynamic properties of each medicine both had more influence on blood vessels than on the heart muscle.

The Panel noted the results of de Champlain *et al* (1998 and 2000). Both papers had shown that administration of amlodipine resulted in a sustained rise in norepinephrine levels suggesting an increase in sympathetic activation. In the discussion section of the earlier paper (de Champlain *et al* 1998) the authors noted that their observations were only carried out with patients supine, for the purpose of standardization of blood sampling and to provide information under basal resting conditions only. Their view was that their results did not allow one to conclude anything about the effects of the treatments on the sympathetic adrenal reactivity of hypertensive patients. The Panel considered, thus, that the clinical significance of de Champlain's results was unknown.

The Panel considered that the claim 'Unlike amlodipine, Adalat LA does not increase the heart rate' was misleading and disparaged amlodipine as alleged. It was unclear whether the increase in heart rate related to a side effect or to the pharmacodynamic properties of the medicines. The clinical relevance of the de Champlain data, with regard to the increase in heart rate observed with amlodipine, was unknown. Breaches of Clauses 7.2 and 8.1 were ruled. The Panel did not consider that the claim promoted Adalat LA in a way that was inconsistent with its summary of product characteristics. No breach of Clause 3.2 was ruled.

The Panel considered that the table on page 3 of the leavepiece, which compared Adalat LA with amlodipine, was covered by these rulings.

The table on page 4 of the leavepiece compared Adalat LA with generic nifedipine. As above the Panel considered that it was unclear as to whether an increase in heart rate related to an adverse event such as tachycardia or was concerned with the pharmacodynamic properties of Adalat LA. A breach of Clause 7.2 was ruled. As above, however, the Panel did not consider that the claim promoted Adalat LA in a way that was inconsistent with its summary of product characteristics. No breach of Clause 3.2 was ruled. The table did not refer to amlodipine and so there could be no disparagement of that product. No breach of Clause 8.1 was ruled.

Complaint received **22 November 2001**

Case completed **27 February 2002**

AVENTIS PASTEUR MSD v GLAXOSMITHKLINE

UK Guidance on Best Practice in Vaccine Administration

Aventis Pasteur MSD complained about a booklet entitled 'UK Guidance on Best Practice in Vaccine Administration'. Published by a public relations agency, it was stated on the inside front cover that 'This initiative has been supported by an educational grant from GlaxoSmithKline' and that the guidance had been developed after consultation with listed contributors who had formed the Vaccine Administration Taskforce (VAT). The front cover included the logos of the Royal College of General Practitioners, The Association of Occupational Health Nurse Practitioners (UK), the Royal College of Nursing, the Community Practitioners and Health Visitors Association and the British Travel Health Association. It was stated that the guidance had been developed and endorsed by these five organisations. Aventis Pasteur MSD also complained about an article entitled 'Best Practice in Vaccine Administration' published in the Nursing Standard (Chiodini 2001).

Aventis Pasteur MSD stated that UK doctors largely delegated vaccine administration to nurses. National guidance on vaccines and immunisation was provided in a publication known colloquially as the 'Green Book' which covered many of the medical aspects of the subject, but gave relatively little practical guidance. UK Guidance on Best Practice in Vaccine Administration aimed to address this. As a result nurses involved in immunisation would warmly receive this type of document. The document appeared credible because of the organisations which had endorsed it. It tried to leverage this by stating that 'The information provided should be used in conjunction with the 'Green Book' …'. The reader was therefore given the impression that it represented official guidance. However, it was stated on the inside cover that the initiative was sponsored by GlaxoSmithKline. In addition, requests for copies were directed to GlaxoSmithKline's public relations company. The document therefore clearly fell under the Code and GlaxoSmithKline presumably took responsibility for its content.

Aventis Pasteur MSD alleged that the section of the booklet entitled 'Choice of needle' brought discredit upon, and reduced confidence in, the pharmaceutical industry in breach of Clause 2. It was stated that wherever possible vaccines should be administered intramuscularly and that the needle should be 25mm long to ensure it reached muscle (in all but the smallest of babies). In addition, it listed 'Recommended choice of needle lengths'. The shortest needle recommended for any patient group was 25mm. Aventis Pasteur MSD provided a table comparing the presentation of its vaccines with those of GlaxoSmithKline. Of the ten Aventis Pasteur MSD products listed, eight had a fixed 16mm needle, one had a detached needle and one was needleless. Of the ten GlaxoSmithKline products listed, two had fixed 16mm needles, two had fixed 25mm needles, three had detached needles and three had no needles.

The vast majority of Aventis Pasteur MSD's vaccines were supplied with a fixed 16mm needle. Its customers could be left with the erroneous impression that none of its vaccines were appropriate for their patients. This was clearly not the case. All Aventis Pasteur MSD's vaccines had been licensed. The licence for a vaccine included not only the vaccine itself but also its presentation (syringe, vial, needle type etc). This 'guidance' attempted to undermine the very licences of Aventis Pasteur MSD's products and brought discredit upon the industry. Aventis Pasteur MSD alleged that this represented disguised promotion. A section entitled 'Technique' under the sub-heading 'Prefilled syringes and ampoules' stated: 'If it is felt that the needle length will not be sufficient to deliver the vaccine to the appropriate site (ie due to a thick layer of fat for IM injection) then an alternative should be sought. Some vaccines are supplied with non-fixed needles or in ampoules, allowing individual choice on needle length'. This clearly promoted vaccines presented with non-fixed needles or in ampoules.

The statement 'Another common misconception is that smaller doses (eg 0.5ml) of vaccine are better tolerated than large doses (eg 1ml) and produce fewer local reactions. However, evidence suggests that both local and systemic reactions at the vaccination site are similar for both 0.5ml and 1ml doses' was alleged by Aventis Pasteur MSD not to be a fair and objective comparison which reflected all the evidence. Three of the four supporting references were not relevant to the current UK marketplace as they concerned DTP or Hib vaccines that were not available as part of the national childhood immunisation programme. The statement was pertinent to hepatitis A vaccines and the fourth reference, Goilav *et al* (1995), concerned this. Aventis Pasteur MSD's hepatitis A vaccine, Avaxim, had a volume of 0.5ml whereas GlaxoSmithKline's Havrix Monodose had a volume of 1ml. Perversely, however, Goilav *et al* referred to an older formulation of Havrix that contained half the antigen content, compared to the current Havrix Monodose but in the same 1ml volume. This would be acceptable were it not for the fact that two other studies did compare Avaxim with Havrix Monodose (Zuckerman *et al* 1997; Zuckerman *et al* 1998). Both of these studies demonstrated significantly better tolerability at the injection site for Avaxim compared to Havrix Monodose.

Aventis Pasteur MSD also complained about an abridged version of the booklet, containing all the issues identified above, which had been published in the Nursing Standard. Despite listing all the people involved in drawing up the guidance, nowhere was it stated that GlaxoSmithKline sponsored the initiative.

The Panel noted that GlaxoSmithKline had sponsored the booklet in question. The original idea for the booklet had come from the company but a taskforce had written it independently of

GlaxoSmithKline. The Panel did not know how members of the taskforce had been selected. The company had been able to make minor amendments to the final text but had not changed any substantive issues. The taskforce had approved all amendments. The booklet did not mention any specific products and was described as outlining 'the step by step process and techniques involved in vaccination from taking a vaccine out of the refrigerator to disposal of the needle and syringe at the end of the procedure'. It stated that the guidance should be used in conjunction with the 'Green Book' and would therefore not go into detail about the individual vaccines. Nurses were recommended to use resources such as the 'Green Book' and the most recent summary of product characteristics or patient information leaflet to update themselves on information relating to a particular disease area or product. GlaxoSmithKline had supplied its representatives with one copy each of the booklet to be used with customers. If customers wanted a copy for themselves these were available on request from GlaxoSmithKline's public relations agency. The Panel considered that GlaxoSmithKline had not sufficiently distanced the provision of the booklet from its promotional activities. Providing a copy to each of its representatives who were discussing its contents with health professionals and making further copies for customers available through its public relations agency meant that the booklet was being used for a promotional purpose and was, therefore, within the scope of the Code.

The first sentence in section 'Choice of needle' stated that 'The correct length and gauge of the needle are key in ensuring that the vaccine is delivered to the correct location as painlessly as possible and with maximum immunogenicity'. Readers were further informed that for an intramuscular injection the needle length should be 25mm. In a highlighted box of text entitled 'Recommended Choice of Needle Lengths' the shortest needle recommended in any patient group was 25mm. It was also suggested that a 25mm needle should be used if an injection was to be given subcutaneously. The Panel noted that the World Health Organization (WHO) in its document relating to global vaccines and immunization recommended a 25mm needle length for all intramuscular or subcutaneous injections. The section in question did not refer to any specific vaccines. General advice regarding needle length was given which was consistent with WHO recommendations. Readers were not told that some vaccines were supplied with a fixed 16mm needle. The Panel noted that the fact that vaccines with 16mm fixed needles were licensed might be seen as a recommendation for that needle length. The section was positive for a 25mm needle length. The Panel did not consider that in its discussion of needle length the booklet brought discredit upon or reduced confidence in the pharmaceutical industry as alleged. No breach of Clause 2 was ruled.

A chapter in the booklet entitled 'Technique' discussed prefilled syringes and ampoules. Readers were told that if they considered that the needle length would not be sufficient to deliver the vaccine to the appropriate site (ie due to a thick layer of fat for IM injection) then an alternative should be sought. It was not stated that some vaccines were supplied with a fixed 16mm needle and others with a fixed 25mm needle. Readers were told however that those vaccines supplied with non-fixed needles or in ampoules, allowed individual choice on needle length. The Panel considered that the information was given in a straightforward, matter-of-fact manner. The reader was not drawn to using GlaxoSmithKline's vaccines in preference to those from other companies. There were no critical reference to other companies' products. The Panel did not consider that the section of the booklet entitled 'Choice of Needle', nor the discussion of prefilled syringes and ampoules, represented disguised promotion for GlaxoSmithKline's products as alleged. No breach of the Code was ruled.

Readers were informed that while it was commonly thought that smaller volume injections (0.5ml) were better tolerated than larger volume injections (1ml) there was evidence to show that both local and systemic reactions at the injection site were similar for both. The Panel considered that the paragraph at issue discussed the matter in general terms; the information given was not specific to any vaccine type. The information was not related solely to a comparison of Havrix and Avaxim. The Panel did not consider that the paragraph was unfair or unobjective as alleged. No breach of the Code was ruled.

The Panel noted that the related article, an abridged version of the booklet which had been published in the Nursing Standard, did not refer to GlaxoSmithKline. A letter from the Nursing Standard confirmed that GlaxoSmithKline had had no involvement in the placement of the article; the journal had received no sponsorship or educational grant from the company. The journal itself had commissioned the article from one of the members of the taskforce that had put the booklet together. The Panel considered that it would have been helpful if the article had declared GlaxoSmithKline's sponsorship of the original initiative but under the circumstances responsibility for this declaration did not lie with the company. No breach of the Code was ruled.

Aventis Pasteur MSD Ltd complained about a spiral bound 76 page booklet entitled 'UK Guidance on Best Practice in Vaccine Administration'. Published in October 2001 by a public relations agency, it was stated on the inside front cover that 'This initiative has been supported by an educational grant from GlaxoSmithKline'. It was further stated that the guidance had been developed in 2001 after consultation with listed contributors who had formed the Vaccine Administration Taskforce (VAT).

The front cover included the logos of the Royal College of General Practitioners, The Association of Occupational Health Nurse Practitioners (UK), the Royal College of Nursing, The Community Practitioners and Health Visitors Association and the British Travel Health Association. Page 4 stated that the guidance had been developed and endorsed by these five organisations.

GlaxoSmithKline stated that the document had been sent to its representatives during the first week of November. Each representative was sent one copy and advised to request further copies from GlaxoSmithKline's distribution centre as necessary. Representatives were instructed to respect the independence of the authorship in discussing any of its contents with customers.

Aventis Pasteur MSD also complained about an article entitled 'Best Practice in Vaccine Administration' published in the Nursing Standard (Chiodini 2001).

COMPLAINT

Aventis Pasteur MSD stated that UK doctors largely delegated vaccine administration to nurses. As such, the nurse assumed professional accountability. There was increasing guidance and legislation in this area. National guidance on vaccines and immunisation was provided in a publication known colloquially as the 'Green Book'. Although this covered many of the medical aspects of the subject, there was relatively little practical guidance. UK Guidance on Best Practice in Vaccine Administration aimed to address this. As a result nurses involved in immunisation would warmly receive this type of document.

Aventis Pasteur MSD stated that the document appeared credible as it was endorsed by the Association of Occupational Health Nurse Practitioners, the British Travel Health Association, the Community Practitioners and Health Visitors Association, the Royal College of General Practitioners and the Royal College of Nursing. It tried to leverage this by stating on page 8 that 'The information provided should be used in conjunction with the 'Green Book' …'. The reader was therefore given the impression that this document represented official guidance. However, it was stated on the inside cover that the initiative was sponsored by GlaxoSmithKline. In addition, requests for copies were directed to an agency which was GlaxoSmithKline's public relations company. The document therefore clearly fell under the Code and GlaxoSmithKline presumably took responsibility for its content.

Aventis Pasteur MSD alleged that the section of the booklet entitled 'Choice of needle' (pages 39-41) brought discredit upon, and reduced confidence in, the pharmaceutical industry in breach of Clause 2.

On page 39 it was stated that wherever possible vaccines should be administered intramuscularly and that the needle should be 25mm long to ensure it reached muscle (in all but the smallest of babies). In addition, box 9 on page 40 listed the 'Recommended choice of needle lengths'. The shortest needle recommended for any patient group was 25mm.

Aventis Pasteur MSD provided a table comparing the presentation of its vaccines with those of GlaxoSmithKline. Of the ten Aventis Pasteur MSD products listed, eight had a fixed 16mm needle, one had a detached needle and one was needleless. Of the ten GlaxoSmithKline products listed, two had fixed 16mm needles, two had fixed 25mm needles, three had detached needles and three had no needles.

It was evident from this comparison that the vast majority of Aventis Pasteur MSD's vaccines were supplied with a fixed 16mm needle. The potential effect of this 'guidance' on Aventis Pasteur MSD's customers could not be underestimated. They could be left with the erroneous impression that none of Aventis Pasteur MSD's vaccines (including those supplied by the NHS as part of the national childhood immunisation programme) were appropriate for their patients, thereby reducing confidence in the pharmaceutical industry. This was clearly not the case. All Aventis Pasteur MSD's vaccines had been licensed in the UK by the Medicines Control Agency as they were presented. In other words, the licence for a vaccine included not only the vaccine itself but also its presentation (syringe, vial, needle type etc). This 'guidance' attempted to undermine the very licences of Aventis Pasteur MSD's products and brought discredit upon the pharmaceutical industry.

Aventis Pasteur MSD alleged that the section of the booklet entitled 'Choice of needle' (pages 39-41) represented disguised promotion in breach of Clause 10.

Aventis Pasteur MSD stated that from the table of data referred to above the result of the 'guidance', were it taken at face value, would be the purchase of only GlaxoSmithKline vaccines (with the exception of paediatric hepatitis A vaccines, hepatitis B vaccines in vials and influenza vaccines). This was further reinforced in the section entitled 'Technique' (pages 43-47), specifically under the sub-heading 'Prefilled syringes and ampoules' which stated:

'…If it is felt that the needle length will not be sufficient to deliver the vaccine to the appropriate site (ie due to a thick layer of fat for IM injection) then an alternative should be sought.

Some vaccines are supplied with non-fixed needles or in ampoules, allowing individual choice on needle length.

Note: *Where it is not possible to change the needle size (ie with fixed needles), the vaccine should never be transferred to another syringe.'*

This clearly promoted vaccines presented with non-fixed needles or in ampoules which, as could be seen from the table summarised above, was further disguised promotion of GlaxoSmithKline products.

Aventis Pasteur MSD alleged that the final paragraph on page 40 breached Clause 7.2 of the Code. It stated:

'Another common misconception is that smaller doses (eg 0.5ml) of vaccine are better tolerated than large doses (eg 1ml) and produce fewer local reactions. However, evidence suggests that both local and systemic reactions at the vaccination site are similar for both 0.5ml and 1ml doses.'

This was supported by four references, three of which were not relevant to the current UK marketplace as they concerned DTP or Hib vaccines that were not available as part of the national childhood immunisation programme. The statement was however particularly pertinent to hepatitis A vaccines and the fourth reference, Goilav *et al* (1995), concerned this. Aventis Pasteur MSD's hepatitis A vaccine,

Avaxim, had a volume of 0.5ml whereas GlaxoSmithKline's Havrix Monodose had a volume of 1ml. Perversely, however, Goilav *et al* referred to an older formulation of Havrix that contained half the antigen content (720 ELU), compared to the current Havrix Monodose (1440 ELU), but in the same 1ml volume. This would be acceptable were it not for the fact that two other published studies did compare Avaxim with Havrix Monodose (Zuckerman *et al* 1997; Zuckerman *et al* 1998). Both of these studies demonstrated significantly better tolerability at the injection site for Avaxim compared to Havrix Monodose. The first study showed statistically significantly fewer local reactions in previously seronegative subjects receiving Avaxim compared to Havrix Monodose. The second study showed statistically significantly fewer subjects experienced pain upon vaccination after receiving Avaxim compared to Havrix Monodose. The latter would seem to be particularly relevant to the issue of volume, since volume was likely to influence immediate pain as the tissues distended.

Aventis Pasteur MSD alleged that this paragraph was therefore not a fair and objective comparison and that it did not reflect all the available evidence in breach of Clause 7.2 of the Code.

Aventis Pasteur MSD stated that due to the serious nature of these issues it strongly believed that this document should be withdrawn forthwith. Unfortunately, however, this might not limit its potential to damage since an abridged version of the booklet, containing all the issues identified above, had already been published in Nursing Standard. Despite listing all the people involved in drawing up the guidance, nowhere was it stated that GlaxoSmithKline sponsored the initiative. This clearly breached Clause 9.9 of the Code. Since this journal publication could not be withdrawn separate action would be necessary to limit its impact. In particular, Aventis Pasteur MSD was concerned that GlaxoSmithKline sales representatives might use this article as a disguised promotional tool and any action taken would need to prevent this.

RESPONSE

GlaxoSmithKline stated that it did not agree that the booklet gave the impression of official guidance. Official immunisation guidance in the UK was contained in the Department of Health publication 'Immunisation Against Infectious Disease', better known as the 'Green Book' (so called because of its green cover). The Green Book was first published in 1988, was now in its fourth edition, and was widely distributed to doctors and nurses in the UK by the Department of Health. The Guidance on Best Practice in Vaccine Administration document had a purple cover, which was very different in appearance to the Green Book, and did not acknowledge any support or endorsement from the Department of Health. The recommendation to use the booklet in conjunction with the Green Book could not be taken to imply that the booklet was official.

GlaxoSmithKline stated that it did not accept that the booklet brought discredit upon, or reduced confidence in, the pharmaceutical industry. The document was prepared as part of the company's commitment to promote good immunisation practice. It met a clear need for practical guidance on vaccine administration, identified in an NOP poll carried out among 500 practice nurses in February 2001.

The authors of the booklet were all independent, respected experts in vaccine administration. Editorial control was wholly independent of GlaxoSmithKline and its public relations agency. The role of GlaxoSmithKline was limited to checking the contents for factual accuracy. The agency was responsible for its production and printing.

The booklet covered the full spectrum of vaccine administration issues (fifteen topics altogether), whereas the only area of concern raised by Aventis Pasteur MSD related to one topic – choice of needle length. The recommendations concerning choice of needle length in the document were evidence based and clearly referenced. Similar recommendations on choice of needle length had been published in other countries, notably the USA and Australia. In addition the World Health Organisation (WHO), as part of its documentation on the expanded programme on immunization (EPI), recommended the use of a long (25mm) needle for all intramuscular and subcutaneous immunisations.

WHO recommendations on needle length were:

i) BCG (for intradermal injections). Syringe size 0.1ml. Needle sizes – reusable 10mm, 26 gauge – single use 10mm, 27 or 28 gauge

ii) All other EPI vaccines (for intramuscular or subcutaneous injections). Syringe size 1.0ml. Needle sizes – reusable 25mm, 22 gauge – single use 25mm, 23 gauge

iii) Reconstitution. Syringe size 5.0ml. Needle size 76mm, 18 gauge.

Aventis Pasteur MSD had provided a table comparing vaccines marketed by it and GlaxoSmithKline. Aventis Pasteur MSD concluded that its customers' confidence would be undermined because the vast majority of its vaccines were supplied with a fixed, short (16mm) needle, and were therefore in breach of the guidelines on choice of needle length. GlaxoSmithKline stated that the table was however incomplete, as comparable data from other UK vaccine manufacturers (Wyeth, Solvay, Baxter, Masta, Chiron, Evans/Powderject) had been omitted, as had some GlaxoSmithKline vaccines. GlaxoSmithKline submitted another table which it stated was more complete; it showed all vaccines marketed in the UK for intramuscular and/or deep subcutaneous use and whether they were affected by the recommendations in the document (ie whether or not they had a fixed 16mm needle). The table showed that:

- of 15 GlaxoSmithKline products, 3 had a fixed 16mm needle, 12 did not
- of 15 Aventis Pasteur MSD products, 13 had a fixed 16mm needle, 2 did not
- of 6 Wyeth products, 1 had a fixed 16mm needle, 5 did not

- of 3 Evans/Powderject products, 2 had a fixed 16mm needle, 1 did not
- 1 Chiron product, 1 Masta product and 1 Baxter product did not have a fixed 16mm needle
- 1 Solvay product had a fixed 16mm needle.

GlaxoSmithKline stated that the booklet did not attempt to challenge the licences of any of these vaccines; rather it sought to promote good clinical practice. Products of several vaccine manufacturers, including GlaxoSmithKline, were affected by the recommendations, not just those of Aventis Pasteur MSD. GlaxoSmithKline marketed three vaccines with a 16mm fixed needle: hepatitis A vaccine for children (Havrix Junior Monodose), hepatitis B vaccine for children (Engerix B paediatric) and influenza vaccine (Fluarix). GlaxoSmithKline also marketed tetanus vaccine produced by Evans/Powderject (Clostet – this was one of the vaccines omitted from Aventis Pasteur MSD's table) which had a fixed 16mm needle. Influenza vaccines from three other manufacturers were also supplied with a fixed 16mm needle: Begrivac (Wyeth), Fluvirin (Evans/Powderject) and Influvac (Solvay).

Vaccine manufacturers were able at any time to change their needle presentations where appropriate; all that was required was a type 1 variation to the existing licences. GlaxoSmithKline had now embarked on a programme to change its vaccine presentations as necessary in line with the guidelines. GlaxoSmithKline noted that the latest addition to the Aventis Pasteur MSD range of vaccines (Viatim, launched in October this year) had a detached needle, thereby allowing choice.

GlaxoSmithKline did not accept that the booklet represented disguised promotion in breach of Clause 10. There was no mention of any products in the booklet. As shown above, products of both Aventis Pasteur MSD and GlaxoSmithKline (and other vaccine manufacturers) were affected by the recommendations in the booklet. The sponsorship provided by GlaxoSmithKline was clearly stated on the inside cover, and was thus obvious from the outset.

GlaxoSmithKline did not accept that the final paragraph on page 40 was misleading in breach of Clause 7.2. The statement in the paragraph was supported by four references, and although the first three of these references concerned DTP or Hib vaccines that were not currently used in the UK national immunisation programme, they were nonetheless still entirely relevant in the context of a general statement concerning vaccine volume and the incidence of local reactions. Indeed the vaccines mentioned in these three supporting references had been used in the UK immunisation programme in the past.

Aventis Pasteur MSD implied that the fourth reference was misleading since it referred to a study of a formulation of a GlaxoSmithKline vaccine, Havrix, that was no longer available and that furthermore there were other references to support better tolerability for the Aventis Pasteur MSD competitor product Avaxim. In support of its argument Aventis Pasteur MSD cited two further references that, in its view, supported superior tolerability of Avaxim compared to Havrix. This very issue, with the same two supporting references, had been the subject of a previous complaint against Aventis Pasteur MSD by SmithKline Beecham, Case AUTH/1008/4/00. At that time the Panel considered that these two references did not support the claim by Aventis Pasteur MSD of superior tolerability of Avaxim compared to Havrix and a breach of Clause 7.2 was ruled. GlaxoSmithKline also noted that Aventis Pasteur MSD had inaccurately cited its second supporting reference (Zuckerman *et al* 1998) in its complaint: the words 'as a booster following primary immunisation with Havrix (1440 EL.U)' had been omitted (the fact that this study related to booster, rather than primary immunisation, was one of the reasons that the Panel considered the reference to be inappropriate at the time of the original complaint).

GlaxoSmithKline accepted that there was no acknowledgement of its sponsorship in the Nursing Standard article. The publication was briefed by GlaxoSmithKline's PR agency prior to the submission of the article regarding GlaxoSmithKline's sponsorship, and GlaxoSmithKline regretted that it did not insist that its sponsorship should be acknowledged in the article.

In response to a request for further information GlaxoSmithKline stated that the original idea for development of the booklet came from the company itself following a piece of market research carried out among practice nurses. GlaxoSmithKline had proposed that the booklet should cover all practice aspects of vaccine administration. The detailed scope and contents of the booklet were subsequently developed entirely by the members of a Vaccine Administration Taskforce, without any influence from the company. A letter from one of the members of the taskforce corroborating this point was provided.

GlaxoSmithKline stated that it had checked the booklet for factual accuracy and made spelling and grammatical amendments. A few minor wording changes were made for clarity eg the word 'vaccinee' was changed to 'patient' and some footnotes were added, for example to draw the reader's attention to an appendix. No substantive issues were changed. The taskforce approved all amendments.

GlaxoSmithKline reiterated that its representatives were each given one copy of the booklet for their own use. Representatives were able to order copies for customers using the company's internal ordering system. Additional copies were available to customers on request from GlaxoSmithKline's public relations agency. Representatives were verbally briefed on the booklet, and asked to respect its independence in discussing its contents with customers. No written briefing material was given to the representatives.

GlaxoSmithKline stated that the Nursing Standard had commissioned the article in that journal. GlaxoSmithKline had had no influence on the article, which was peer reviewed, and provided no sponsorship for its publication. A letter from the journal which described events that took place prior to the publication of the article was provided.

PANEL RULING

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The booklet in question had been sponsored by GlaxoSmithKline. The original idea for the booklet had come from the company and it had proposed that it should cover all aspects of vaccine administration. A taskforce had subsequently written the booklet independently of GlaxoSmithKline. The Panel did not know how members of the taskforce had been selected. The company had been able to make minor amendments to the final text but had not changed any substantive issues. The taskforce had approved all amendments. The booklet did not mention any specific products and was described as outlining 'the step by step process and techniques involved in vaccination from taking a vaccine out of the refrigerator to disposal of the needle and syringe at the end of the procedure'. Page 8 of the booklet stated that the guidance should be used in conjunction with the 'Green Book' and would therefore not go into detail about the individual vaccines. Nurses were recommended to use resources such as the 'Green Book' and the most recent summary of product characteristics or patient information leaflet to update themselves on information relating to a particular disease area or product. GlaxoSmithKline had supplied its representatives with one copy each of the booklet to be used with customers. If customers wanted a copy of the booklet for themselves these were available on request from GlaxoSmithKline's public relations agency. The Panel considered that GlaxoSmithKline had not sufficiently distanced the provision of the booklet from its promotional activities. Providing a copy to each of its representatives who were discussing its contents with health professionals and making further copies for customers available through its public relations agency meant that the booklet was being used for a promotional purpose and was, therefore, within the scope of the Code.

Pages 39-41 referred to 'Choice of needle'. The first sentence in this section stated that 'The correct length and gauge of the needle are key in ensuring that the vaccine is delivered to the correct location as painlessly as possible and with maximum immunogenicity'. Readers were further informed that for an intramuscular injection the needle length should be 25mm. In a highlighted box of text entitled 'Recommended Choice of Needle Lengths' the shortest needle recommended in any patient group was 25mm. It was also suggested that a 25mm needle should be used if an injection was to be given subcutaneously. The Panel noted that the WHO in its document relating to global vaccines and immunization 'Module 4 Ensuring safe injections' recommended a 25mm needle length for all intramuscular or subcutaneous injections.

The Panel noted that the section of the booklet in question did not refer to any specific vaccines. General advice regarding needle length was given which was consistent with WHO recommendations. Readers were not told that some vaccines were supplied with a fixed 16mm needle. The Panel noted that the fact that vaccines with 16mm fixed needles were licensed might be seen as a recommendation for that needle length. The section was positive for a 25mm needle length. The Panel did not consider that in its discussion of needle length the booklet brought discredit upon or reduced confidence in the pharmaceutical industry as alleged. No breach of Clause 2 was ruled.

The Panel noted that nowhere in the booklet was any specific vaccine mentioned. The section on choice of needle recommended a 25mm needle for most patient groups and injection routes. A chapter in the booklet entitled 'Technique' discussed prefilled syringes and ampoules. Readers were told that if they considered that the needle length would not be sufficient to deliver the vaccine to the appropriate site (ie due to a thick layer of fat for IM injection) then an alternative should be sought. It was not stated that some vaccines were supplied with a fixed 16mm needle and others with a fixed 25mm needle. Readers were told however that those vaccines supplied with non-fixed needles or in ampoules, allowed individual choice on needle length. The Panel considered that the information was given in a straightforward, matter-of-fact manner. The reader was not drawn to using GlaxoSmithKline's vaccines in preference to those from other companies. There were no critical reference to other companies' products. The Panel considered that the booklet was clearly about, as stated in its title, '… Best Practice in Vaccine Administration'. The Panel did not consider that the section of the booklet entitled 'Choice of Needle' (pages 39-41), nor the discussion of prefilled syringes and ampoules, represented disguised promotion for GlaxoSmithKline's products as alleged. No breach of Clause 10.1 was ruled.

The final paragraph on page 40 informed readers that while it was commonly thought that smaller volume injections (0.5ml) were better tolerated than larger volume injections (1ml) there was evidence to show that both local and systemic reactions at the injection site were similar for both. The Panel considered that the paragraph at issue discussed the matter in general terms; the information given was not specific to any vaccine type. The information was not related solely to a comparison of Havrix and Avaxim. The Panel did not consider that the paragraph was unfair or unobjective as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that the related article, an abridged version of the booklet, which had been published in the Nursing Standard, did not refer to GlaxoSmithKline. A letter from the Nursing Standard confirmed that GlaxoSmithKline had had no

involvement in the placement of the article; the journal had received no sponsorship or educational grant from the company. The journal itself had commissioned the article from one of the members of the taskforce that had put the booklet together. The Panel considered that it would have been helpful if the article had declared GlaxoSmithKline's sponsorship of the original initiative but under the circumstances responsibility for this declaration did not lie with the company. No breach of Clause 9.9 was ruled.

During its consideration of this case the Panel noted that the declaration of GlaxoSmithKline's sponsorship of the booklet was stated in small italic print on the inside front cover. The front cover itself featured the logos of the five professional bodies that had endorsed the booklet. The Panel considered that GlaxoSmithKline's declaration of sponsorship should have been on the front cover so that, as required by Clause 9.9 of the Code, readers were aware of the company's involvement 'at the outset'. There was no allegation of a breach of the Code in this regard but the Panel requested that GlaxoSmithKline be advised of its views.

Complaint received **26 November 2001**

Case completed **22 February 2002**

CASE AUTH/1260/12/01

ASTRAZENECA v WYETH

Promotion of Prostap

AstraZeneca complained about the promotion of Prostap (leuprorelin) by Wyeth. Prostap was presented as a prolonged release powder for suspension for injection by subcutaneous or intramuscular administration after reconstitution. The items at issue were two detail aids and two leavepieces. AstraZeneca supplied Zoladex (goserelin) which was presented as an implant in a prefilled syringe. Both Prostap and Zoladex were to be administered once a month.

Both detail aids and one of the leavepieces contained bar charts headed 'Comparison of pain associated with Prostap and goserelin injections'. The bar charts were referenced to a six month study by Beese (2000) in which patients received two Zoladex injections over an eight week run-in period after which they were either switched to Prostap (Group A) or continued on Zoladex (Group B) for a further eight weeks. Patients were then crossed over on to the alternative therapy for a further two injections. The bar charts showed the pain score for each injection in each group. The bar chart for Group A showed a score of 1.27 for Zoladex vs 0.64 for Prostap. For Group B the scores were 0.55 and 0.15 respectively. The difference between the treatments was statistically significant for both groups (p=0.003). Readers were told that the results related to 'Pain score (visual analogue scale)'.

AstraZeneca noted that the visual analogue score system had a scale of 0-10 (0 signifying no pain). However the bar chart only gave a range from 0 to 1.27. Although a pain score for Zoladex of 1.27 was statistically significantly greater than the score of 0.64 for Prostap, the difference had been visually distorted through the incompleteness of the bar chart. Such an intentional exaggeration consequently portrayed a misleading message with regard to the difference in pain patients experienced between Prostap and Zoladex.

The Panel noted that although the bar chart gave the pain score for each injection, and explained how pain had been assessed, there was no information to allow the reader to put the scores into context. The Panel considered that the lack of information about the scoring system meant that the bar charts were misleading. Breaches of the Code were ruled.

The claim 'Acceptability of interchanging the products raises the possibility of switching goserelin patients onto the more patient-friendly Prostap' was the last bullet point on a page in one of the detail aids headed 'Patients prefer Prostap' and subheaded 'A recent study compared the tolerability of Prostap SR and goserelin acetate'. The study referred to was Beese (2000) and a bar chart depicting pain score upon injection of the two medicines was shown (as considered above). A similar claim 'Patients showed overall acceptability of interchanging the two treatments, raising the possibility of switching goserelin patients onto the more patient-friendly Prostap' appeared in association with the same heading, subheading and bar chart on the front page of one of the leavepieces.

AstraZeneca alleged that the claim inferred that Zoladex was a less patient-friendly product than Prostap. Pain on administration was one measure of how 'patient-friendly' a medicine was but other aspects of tolerability such as frequency of administration, co-administration requirements, and side effects must also be evaluated and taken into account. No head-to-head studies had been conducted to assess how Zoladex and Prostap compared in terms of these other aspects of tolerability. The claim in question was based upon the conclusion of a small (n=22) open study which specifically looked at patient tolerance of pain when injected with either Prostap or Zoladex (Beese 2000). No other effects were considered. However the subheading on the detail aid gave the incorrect impression that overall tolerability had been compared. To suggest tolerability was being

compared was an exaggeration of the study design and so likely to exaggerate the implication of its results. AstraZeneca alleged that using the results of this study to support the claim that Prostap was more patient-friendly than Zoladex was inaccurate and unfair and likely to mislead. Furthermore, the Prostap and Zoladex summaries of product characteristics (SPCs) listed '… irritation at the injection site' and 'Occasional local reactions include mild bruising at the subcutaneous injection site' respectively. In fact both were very similar in terms of listed undesirable effects which clearly indicated highly comparable tolerability profiles. AstraZeneca alleged that the claim was an unsubstantiated critical reference.

The Panel considered that patient tolerability was based upon a number of factors one of which, with regard to Prostap and Zoladex, would be patients' perception of pain upon injection. Beese had evaluated one aspect of tolerability of the two medicines but had not compared overall tolerability. No clinical data directly comparing the products in relation to overall tolerability had been submitted. The Panel considered that although the pain score results had been given, readers would nonetheless assume that 'tolerability' and 'patient-friendly' related to more than that. The Panel considered the claim misleading; a breach of the Code was ruled. The Panel did not consider that the claim disparaged Zoladex; no breach of the Code was ruled in that regard.

The claim 'goserelin acetate – Often requires local anaesthetic' appeared as the last point in a highlighted box of text which listed its physical properties and method of administration. The box of text appeared in both a detail aid and a leavepiece and in each case was alongside a box of text which listed comparable details for Prostap. AstraZeneca stated that the claim appeared where the tolerability of both Prostap and Zoladex were directly compared. AstraZeneca noted that the SPC for Zoladex made no mention of the need to co-administer a local anaesthetic. The Zoladex SPC had previously included a statement advising that, if desired, a local anaesthetic could be given concomitantly but evidence from post-marketing clinical studies had shown that owing to an improvement in needle design of Zoladex, the administration of local anaesthetic was not necessary. This evidence was sufficient to have the SPC amended to remove the advice. In light of this, the above claim was therefore unsubstantiated and inaccurate. The message was contrary to the Zoladex SPC and was misleading. It was also a critical reference to Zoladex which was incapable of substantiation.

The Panel noted that there was no requirement in the Zoladex SPC that the injection should be co-administered with a local anaesthetic. Wyeth had referred to DIN-Link data which showed that 16.4% of Zoladex/Zoladex LA was co-prescribed with a local anaesthetic, although this data had not been provided. Nonetheless the Panel did not consider that 16.4% of prescriptions justified a claim of 'often'. The Panel also noted that the DIN-Link data related to the combined total use of Zoladex and Zoladex LA. It was unclear to which product the claim at issue related, Zoladex or Zoladex LA. The Panel considered that the claim was misleading, had not been substantiated and disparaged Zoladex. Breaches of the Code were ruled.

AstraZeneca UK Limited complained about the promotion of Prostap (leuprorelin) by Wyeth. Prostap was presented as a prolonged release powder for suspension for injection by subcutaneous or intramuscular administration after reconstitution. The promotional items at issue were two detail aids (refs ZPR0636 and ZPR0662) and two leavepieces (refs ZPR0664 and ZPR0682). AstraZeneca supplied Zoladex (goserelin) which was presented as an implant in a prefilled syringe. Both Prostap and Zoladex were to be administered once a month.

1 Comparison of pain associated with Prostap and Zoladex injections

Both detail aids and one of the leavepieces (ZPR0664) contained bar charts headed 'Comparison of pain associated with Prostap and goserelin injections'. The bar charts were referenced to a six month study by Beese (2000) in which 22 patients had received two Zoladex injections over an eight week run-in period after which they were either switched to Prostap (Group A) or continued on Zoladex (Group B) for a further eight weeks. Patients were then crossed over on to the alternative therapy for a further two injections. The bar charts showed the pain score for each injection in each group. The bar chart for Group A showed a score of 1.27 for Zoladex vs 0.64 for Prostap. For Group B the scores were 0.55 and 0.15 respectively. The difference between the treatments was statistically significant for both groups (p=0.003). Readers were told that the results related to 'Pain score (visual analogue scale)'.

COMPLAINT

AstraZeneca noted that the supplementary information for Clause 7.8 of the Code stated that particular care should be taken with graphs and tables to ensure that they did not mislead, for example by their incompleteness or unusual scales.

The bar chart presented results from a study measuring level of pain experienced by patients receiving either a Prostap or Zoladex injection. The degree of pain was assessed using a visual analogue score system with a scale of 0-10 (0 signifying no pain). However the vertical axis of the bar chart, which represented pain score, did not show the full scale but instead only gave a range from 0 to 1.27.

Although a pain score of 1.27 recorded for Zoladex was statistically significantly greater than a score of 0.64 recorded for Prostap, such a difference had been visually distorted through the incompleteness of the bar chart. Such an intentional exaggeration consequently portrayed a misleading message to the intended audience with regard to the difference in pain patients experienced between Prostap and Zoladex.

AstraZeneca alleged that the graph breached Clauses 7.2 and 7.8 of the Code.

RESPONSE

Wyeth did not accept the allegation that the bar chart comparison had been visually distorted. The bars were of accurate length, and the size of the effect was numerically written in the bars for clarity. Wyeth stated that subsequent to discussions with AstraZeneca, it had modified its materials to include the wording 'visual analogue scale (scale 0-10)'. Clearly, when studying needle pain (as opposed to, say, post-operative pain), the pain scores would be in the lower end of the range 0-10. Nevertheless, from the patient's perspective such pain was still important, as was the fact that the pain score for Zoladex was at least double that for Prostap – a statistically significant difference. Regarding the vertical axis not showing the full 0-10 scale, this was not unusual, as most scientific papers limited the scale in order to assist data interpretation and clarity. Wyeth understood that AstraZeneca would wish to portray these data as a 'misleading message', but this was simply not the case. Wyeth therefore refuted the allegation of breaches of Clauses 7.2 and 7.8.

PANEL RULING

The Panel noted that although the bar chart gave the pain score for each injection, and explained that pain had been assessed using a visual analogue scale, there was no information to allow the reader to put the scores into context. It had not been stated that the visual analogue scale was from 0 to 10; nor had it been explained what points along the scale actually meant in terms of a qualitative description of pain. The Panel considered that the lack of information about the scoring system used meant that the bar charts were misleading. Breaches of Clauses 7.2 and 7.8 were ruled.

2 Claim 'Acceptability of interchanging the products raises the possibility of switching goserelin patients onto the more patient-friendly Prostap'

This claim appeared as the last bullet point on a page of the detail aid (ZPR0662) headed 'Patients prefer Prostap' and subheaded 'A recent study compared the tolerability of Prostap SR and goserelin acetate'. The study referred to was Beese (2000) and a bar chart depicting pain score upon injection of the two medicines was shown (point 1 above). A similar claim 'Patients showed overall acceptability of interchanging the two treatments, raising the possibility of switching goserelin patients onto the more patient-friendly Prostap' to the claim in question also appeared in association with the same heading, subheading and bar chart on the front page of a leavepiece (ZPR0682).

COMPLAINT

AstraZeneca stated that in both the detail aid and the leavepiece the claim inferred that Zoladex was a less patient-friendly product than Prostap.

To accurately establish whether a medicine was 'patient-friendly' must depend upon a number of measurable parameters of which pain on administration was just one. Other aspects of tolerability such as frequency of administration, co-administration requirements, and side effects must also be evaluated and taken into account. However in relation to Zoladex and Prostap no head-to-head studies had been conducted to assess how these products compared in terms of these other aspects of tolerability.

The claim in question was based upon the conclusion of a small (n=22) open study which specifically looked at patient tolerance of pain when injected with either Prostap or Zoladex (Beese 2000). No other product characteristics or effects were considered. However the subheading on the detail aid gave the incorrect impression that overall tolerability had been compared despite the fact that the study only focussed on one aspect of tolerability ie pain on injection. To suggest tolerability was being compared was an exaggeration of the study design and therefore likely to exaggerate the implication of its results.

AstraZeneca alleged that using the results of this study to support the claim that Prostap was more patient-friendly than Zoladex was inaccurate and unfair and likely to mislead the reader, in breach of Clause 7.2.

Furthermore sections 4.8, Undesirable Effects, of the Prostap and Zoladex summaries of product characteristics (SPCs) listed '… irritation at the injection site' and 'Occasional local reactions include mild bruising at the subcutaneous injection site' respectively. In fact both these sections as a whole were very similar in terms of listed undesirable effects which clearly indicated that both products had a highly comparable tolerability profile.

AstraZeneca alleged that, in light of this lack of significant difference between products and the absence of conclusive evidence demonstrating that, compared with Zoladex, Prostap was more patient-friendly, the above claim additionally constituted an unsubstantiated critical reference in breach of Clause 8.1.

RESPONSE

Wyeth agreed that pain on administration was one of a number of measurable parameters that influenced the 'patient-friendliness' of a product. There was only one comparative trial of Prostap vs Zoladex with respect to needle pain, which was in Prostap's favour. Until AstraZeneca provided data that showed superiority of Zoladex in an endpoint that would shift the balance of Zoladex's 'patient-friendliness' in its favour, Wyeth believed its wording to be appropriate and balanced. Regarding the use of the word 'tolerability', it was clearly implicit that this referred to tolerance of pain due to the bullet points and figure which followed it. It was highly unlikely that the reader would be misled into believing that 'tolerability' meant 'overall tolerability'.

Wyeth therefore refuted the allegation of breaches of Clauses 7.2 and 8.1.

PANEL RULING

The Panel considered that the patient tolerability of any medicine was based upon a number of factors.

One aspect of patient tolerability with regard to Prostap and Zoladex would be patients' perception of pain upon injection. The study by Beese had, therefore, evaluated one aspect of tolerability of the two medicines but had not compared their overall tolerability. No clinical data directly comparing the products in relation to overall tolerability had been submitted.

The Panel considered that although the pain score results had been given readers would nonetheless assume that 'tolerability' and 'patient-friendly' related to more than that. The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

The Panel did not consider that the claim disparaged Zoladex as alleged. No breach of Clause 8.1 was ruled.

3 Claim 'goserelin acetate – Often requires local anaesthetic'

This claim appeared as the last point in a highlighted box of text which listed the physical properties and method of administration of goserelin acetate. The box of text appeared in both the detail aid (ZRP0662) and the leavepiece (ZPR0682) and in each case was alongside a box of text which listed comparable details for Prostap.

COMPLAINT

AstraZeneca stated that the above claim appeared in the detail aid and the leavepiece where the tolerability of both Prostap and Zoladex were directly compared.

AstraZeneca noted that the SPC for Zoladex made no mention of the need to co-administer a local anaesthetic. Previous versions of the Zoladex SPC had, however, included a statement advising health professionals that, if desired, a local anaesthetic could be given concomitantly. However, evidence from post-marketing clinical studies had shown that, owing to an improvement in needle design of Zoladex, the administration of local anaesthetic was not necessary. This evidence when presented to marketing authorities provided sufficient justification to have such advice removed from the SPC. In light of this, the above claim was therefore unsubstantiated and inaccurate. The message was contrary to the advice in the Zoladex SPC and consequently portrayed a misleading message. AstraZeneca stated that in its opinion such material breached Clauses 7.4 and 7.2. Furthermore, critical reference to Zoladex which was incapable of substantiation rendered the claim in breach of Clause 8.1.

RESPONSE

Wyeth stated that in a teleconference with AstraZeneca, it had offered to change 'often' to 'may' in future promotional materials, which it had done. According to DIN-Link data for the moving annual total ending June 2001, 16.4% of Zoladex/Zoladex LA scrips were co-prescribed with a local anaesthetic. Wyeth therefore submitted that 'may' was readily substantiable, and not in breach of Clause 8.1.

PANEL RULING

The Panel noted that there was no requirement in the Zoladex SPC that the injection should be co-administered with a local anaesthetic. Wyeth had referred to DIN-Link data which showed that 16.4% of Zoladex/Zoladex LA was co-prescribed with a local anaesthetic although this data had not been provided. Nonetheless the Panel did not consider that 16.4% of prescriptions justified a claim of 'often'. The Panel also noted that the DIN-Link data related to the combined total use of Zoladex and Zoladex LA. It was unclear to which product the claim at issue related, Zoladex or Zoladex LA. The Panel considered that the claim was misleading and that it had not been substantiated. The Panel also considered that the claim disparaged Zoladex. Breaches of Clauses 7.2, 7.4 and 8.1 were ruled.

* * * * *

During its consideration of this case the Panel noted that there were two presentations of Prostap – Prostap SR to be administered monthly and Prostap 3 to be administered once every three months. Similarly Zoladex was available to be given once a month (Zoladex) or once every three months (Zoladex LA). The Panel was concerned that data for these products appeared to be mixed and matched throughout the detail aids and leavepieces. For example the Beese data related to the monthly administration of both Prostap and Zoladex, and yet appeared in association with claims for Prostap 3 – in the detail aid (ZPR0662) the data was presented on page 5 which carried the Prostap 3 logo and the strapline 'Patients prefer it' and in the leavepiece (ZPR0664) the data appeared directly beneath a claim specifically related to Prostap 3. The Panel considered that the juxtaposing of such data might be misleading and requested that Wyeth be advised of its concerns in this regard.

Complaint received **5 December 2001**

Case completed **1 March 2002**

CASE AUTH/1261/12/01

SCHERING-PLOUGH v UCB PHARMA

Promotion of Xyzal

Schering-Plough complained about the promotion of Xyzal (levocetirizine) by UCB Pharma. Xyzal was indicated for the symptomatic treatment of allergic conditions such as seasonal allergic rhinitis (including ocular symptoms), perennial allergic rhinitis and chronic idiopathic urticaria. Schering-Plough's product Clarityn (loratadine) was similarly indicated. Xyzal was related to UCB's product Zirtek (cetirizine), a racemic mixture consisting of active levocetirizine and inactive dextrocetirizine.

Schering-Plough alleged that the claim in a leavepiece 'Xyzal gives a higher response rate than loratadine in allergic rhinitis' was misleading and disparaging as the referenced study, Horak *et al* (2001), related to volunteers with only perennial allergic rhinitis exposed to allergen in a Vienna Challenge Chamber. The claim suggested that the study had results in all forms of allergic rhinitis including seasonal allergic rhinitis. This was not so. Schering-Plough was unable to find where the abstract stated that Xyzal had a higher response rate than loratadine. Although there appeared to be a numerical difference between the two products, statistical analysis was lacking. The Panel noted that Horak *et al* (2001) concluded that both loratadine and levocetirizine gave significant control of allergic symptoms caused by exposure to house dust mites under controlled conditions and suggested a faster onset of action of levocetirizine. There was no statistical analysis of the differences between the two. The Panel noted the Horak data on file looked at 73 subjects in relation to seasonal allergic rhinitis. Levocetirizine was shown to be statistically superior to loratadine over the time interval. The Panel considered that the claim was a broad claim which was misleading. The data did show a difference between the products but the difference had not been supported by the statistics with regard to perennial allergic rhinitis. There was no clinical data. The comparison was misleading and disparaged loratadine and breaches of the Code were ruled.

Schering-Plough alleged that it was inaccurate to claim that levocetirizine was a 'new' cetirizine. A new medicine developed from Zirtek, perhaps, but not 'the new cetirizine'. The Panel noted that levocetirizine was one of the constituent parts of cetirizine which was a racemic mixture. The Panel did not consider that the claim was exaggerated or all embracing. It did not imply a special merit that could not be substantiated. The Panel ruled no breach of the Code.

Schering-Plough did not agree with the rationale for a claim 'Xyzal inherits the established safety profile of Zirtek'. While levocetirizine was an enantiomer of the racemic mixture of cetirizine, Xyzal remained a different medicine from Zirtek. Schering-Plough alleged that it was inaccurate for a new medicine, with a black triangle, without the years of pharmacovigilance data Zirtek had, different in at least one constitutive element from Zirtek to attempt to don the mantle of Zirtek's safety profile. The Panel noted that Xyzal was subject to special reporting in relation to adverse reactions; this was what was meant by the inverted black triangle symbol. The Panel noted UCB's submission regarding the similarities between the summaries of product characteristics (SPCs) for Zirtek and Xyzal and Zirtek's established safety profile. The Panel considered nevertheless that the claim was misleading. Despite the similarities it was not yet known whether Xyzal would inherit the established safety profile of Zirtek. The Panel considered that the claim was not capable of substantiation by clinical experience and exaggerated as alleged. Breaches of the Code were ruled.

Schering-Plough alleged that the bullet point '…potent purified isomer' was linked with the strapline 'Refined with power' by a series of clinical claims. This linkage gave rise to the impression that the *in vitro* potency was in some way related to these clinical claims. As there was no clinical data to suggest that Xyzal was more clinically powerful, ie more effective than Zirtek, this strapline was alleged to be misleading. The Panel considered that the claim implied that Xyzal was more clinically powerful than Zirtek. There was no data in this regard. The dose had been reduced from 10mg Zirtek to 5mg Xyzal. This did not necessarily mean that Xyzal had more clinical power than Zirtek. The Panel noted the supplementary information that claims for superior potency in relation to weight were generally meaningless and best avoided unless they could be linked to some practical advantage. The Panel considered that the claim was misleading and a breach of the Code was ruled.

With regard to an announcement from 'e-news' of doctorsworld.com, Schering-Plough alleged that the claim 'Clinical studies have shown that Xyzal is at least as effective as Zirtek, as well as being effective in relieving nasal congestion' was clearly a clinical claim which should be supported by a clinical study. In this regard it had been sent a paper in which the pharmacodynamic properties of levocetirizine in 18 healthy volunteers were reported which would not suffice to support the claim. The Panel noted that the claim was referenced to a clinical study by Potter *et al* (data on file) a placebo-controlled double-blind study on levocetirizine 5mg in the treatment of perennial allergic rhinitis. A statistically significant improvement in the individual symptom scores, particularly in nasal congestion, was observed. There appeared to be no clinical data for nasal congestion associated with seasonal allergic rhinitis. The Panel considered that the claim implied that Xyzal was highly effect in relieving nasal congestion in both seasonal and perennial allergic rhinitis. This had not been demonstrated. A breach of the Code was ruled.

Schering-Plough alleged that a claim 'Comparative studies have shown a higher clinical response rate than Clarityn … in allergic rhinitis, and a more pronounced and longer lasting inhibition of histamine mediated wheal and flare skin reactions

than both Clarityn 10mg and Telfast …', which was referenced to an *in vitro* study, in the midst of clinical claims, implied that this finding had some clinical relevance. The Panel noted that the first part of the claim was a clinical claim and the second part of the claim was referenced to a study by Grant *et al* which was carried out on 18 men with no known allergies. The Panel considered that the claim implied that there was clinical data showing an advantage for Xyzal with regard to wheal and flare skin reactions over 24 hours. This was not so. The basis for this part of the claim had not been made sufficiently clear. The claim was misleading in this regard and a breach of the Code was ruled.

Schering-Plough alleged that it was an exaggeration to state 'There is no evidence that Xyzal impairs mental alertness, reaction times or the ability to drive'. The SPC stated that 'comparative clinical trials have revealed no evidence' which was not quite the same thing. Additionally the SPC stated 'Slightly sedating adverse reactions such as somnolence, fatigue and asthenia were altogether more common (10.2%) than after placebo (4.4%)'. The Panel noted the statements in the Xyzal SPC and considered that the claim at issue did not put the objective measurements of sedation, ie how a patient reacted, into context with the subjective measurements, ie how a patient felt. In this regard the Panel considered that the claim was misleading in breach of the Code.

The Panel considered that the announcement from 'e-news' was an advertisement and a clear prominent statement as to where the prescribing information could be found should have been included. The Panel ruled a breach of the Code as alleged.

Schering-Plough alleged that the claim 'Comparative studies have shown a higher clinical response rate than Clarityn in allergic rhinitis' was inaccurate on at least three counts. Firstly, the use of the word 'studies' implied that a number of studies had all reached the same conclusion; there was only one study. Secondly, the Horak *et al* 2001 study was a volunteer study in 39 individuals with perennial allergic rhinitis exposed to allergen. The use of the word 'clinical' implied this was a more real life setting than a volunteer study. Thirdly, the use of the term 'allergic rhinitis' implied that the results related to all forms of allergic rhinitis, including seasonal allergic rhinitis, when only volunteers with perennial allergic rhinitis were tested. The Panel considered that a previous ruling also applied to the claim now at issue. In addition a breach was ruled as the claim was not capable of substantiation as alleged.

With regard to a detail aid, Schering-Plough alleged that the claim 'Xyzal only contains the levocetirizine enantiomer' was inaccurate as Xyzal also contained excipients. The Panel considered that health professionals would not be misled by the claim. Medicines would be expected to include ingredients other than the active ingredient. No breach of the Code was ruled.

Schering-Plough noted that the claim 'High rate of response in Allergic Rhinitis' was again referenced to Horak *et al* (2001) which was a study in volunteers with perennial rhinitis. This study had no relation to other forms of allergic rhinitis such as seasonal allergic rhinitis. To suggest that approximately 85% of patients, with any kind of allergic rhinitis, would respond to Xyzal was inaccurate. The Panel noted that Schering-Plough had misquoted the claim which actually stated 'High rate of responders in Allergic Rhinitis'. The Panel considered that the Horak study (2001) and the Horak data on file showed a high rate of responders in perennial and seasonal allergic rhinitis respectively. The page was only referenced to Horak *et al* (2001) and not also to the Horak data on file. The Panel did not consider that the claim was misleading or exaggerated as alleged and ruled no breach of the Code.

Schering-Plough alleged that the claim 'Faster than loratadine at relieving nasal symptoms' was also based on the Horak *et al* (2001) study. The conclusion of the report was 'This study … suggests a faster onset of action of levocetirizine'. No statistical comparison of the time of onset of levocetirizine against loratadine was made. In addition the claim appeared to suggest that Xyzal was faster at relieving nasal symptoms in all conditions including, for example, seasonal allergic rhinitis. No evidence was put forward for this all embracing claim. The Panel referred to its previous comments on Horak *et al* (2001). The Panel noted that the claim was referenced to a study on subjects with perennial allergic rhinitis. There was no data with regard to nasal symptoms for seasonal allergic rhinitis. The comparison in the study in question was between loratadine and placebo and levocetirizine and placebo. There was no comparison between levocetirizine and loratadine. The Panel ruled breaches of the Code as the claim was not fair, it was a misleading comparison and was not capable of substantiation.

Schering-Plough noted that the claims 'Highly predictable response' and 'Xyzal displays low intersubject variability' were referenced to a study by Grant *et al* (2001) which was a study on 18 healthy volunteers. Nowhere in the leavepiece was this study population mentioned. This gave the impression of a medicine with predictable pharmacokinetics over a whole spectrum of patients when it had only been tested in a highly homogenous volunteer population which was likely to have a low intersubject variability. Schering-Plough alleged that the claims were misleading. The Panel noted that the page did not make it clear that the data was obtained from 18 healthy male volunteers aged 18 - 54. The Panel noted that Xyzal was licensed for children aged 6 - 12 years as well as adolescents and adults. The data referred to did not cover the entire patient population. The Panel ruled that the claims were misleading.

Schering-Plough alleged that without qualification readers were likely to consider the claim 'More effective than Zirtek' to mean that Xyzal was more clinically effective than Zirtek. However the only data produced was for histamine-induced skin reaction. This model was of extremely doubtful

significance in chronic idiopathic urticaria, and was of no relevance in perennial or seasonal allergic rhinitis. The claim implied a clinical effect from pre-clinical data. The Panel noted that the Devalia *et al* (2001) study was carried out on 18 male healthy volunteers aged 18-41 years. None of the volunteers were skin prick test positive to any of the common allergens. All demonstrated a histamine-induced mean skin wheal diameter of >8mm by skin prick test. With the exception of AUC inhibition of wheal there were no significant differences in percentage of maximum inhibition, time of maximum inhibition, onset time, end time and duration of inhibition of the wheal or flare for the two compounds. The study concluded that levocetirizine 2.5mg had comparable antihistaminic activity to cetirizine 5mg. The doses were not the licensed doses for the products. The Panel considered that the implication was that clinically Xyzal was more effective than Zirtek. There was no data to support such a claim and a breach of the Code was ruled.

Schering-Plough alleged that the claim 'In objective tests of psychomotor function, the incidence of sedation with Xyzal was similar to placebo' was at variance to Section 4.8 of the Xyzal SPC which stated 'Slightly sedating adverse reactions such as somnolence, fatigue, and asthenia were thus altogether more common (10.2%) [after Xyzal] than after placebo (4.4%)'. The Panel noted a previous relevant ruling above. The Panel considered that the claim did not reflect all the evidence: the results of subjective tests of sedation had not been stated. In this regard the Panel noted Section 4.8 of the Xyzal SPC. The claim was misleading and a breach of the Code was ruled.

With regard to a claim 'No impairment of daily activities', Schering-Plough stated that it could not find, nor could UCB supply, any data related to a clinical trial examining any measurement of 'daily activity' except for the ability to drive. The Panel noted its previous relevant rulings. The claim did not reflect the statements in the SPC. The Panel considered that the claim was all embracing as alleged and a breach of the Code was ruled.

With regard to a Xyzal Condensed Product Summary, Schering-Plough alleged that throughout the section 'Chronic Idiopathic Urticaria', much was made of the use of the histamine-induced wheal and flare as 'a surrogate endpoint for urticarial lesions'. Schering-Plough stated that the text stated that 'levocetirizine was statistically superior to loratadine for wheal and flare response' and mentioned the 'high potency and predictability of levocetirizine in inhibiting wheal and flare reactions compared to mizolastine, fexofenadine, loratadine and ebastine'. The prominence given to pre-clinical data appeared designed to suggest a clinical difference in activity between Xyzal and other antihistamines. The Panel noted that the page was devoted to the view that a histamine-induced wheal and flare could be considered as a surrogate endpoint for urticarial lesions. The data was on volunteers. The Panel considered that the applicability of the wheal and flare test in volunteers with no history of allergy to the treatment of patients with chronic idiopathic urticaria was not as clear cut as implied by UCB. The data was more limited than the impression given. It was not immediately clear that the results shown did not relate to patients. The laser-doppler images shown implied that Xyzal 5mg would be more effective in treating chronic idiopathic urticaria than Zirtek 10mg. There was no clinical data to support this. The Panel considered that in this regard the page was misleading. Breaches of the Code were ruled.

Schering-Plough Limited complained about the promotion of Xyzal (levocetirizine) by UCB Pharma Limited.

Xyzal was indicated for the treatment of symptoms associated with allergic conditions such as: seasonal allergic rhinitis (including ocular symptoms); perennial allergic rhinitis and chronic idiopathic urticaria. Schering-Plough's product Clarityn (loratadine) was similarly indicated. Xyzal was related to UCB's product Zirtek (cetirizine), a racemic mixture consisting of active levocetirizine and inactive dextrocetirizine. The licensed dose of Zirtek was 10mg per day. The licensed dose of Xyzal was 5mg per day.

A Xyzal leavepiece

The two page leavepiece (ref UCB-XYZ-01-05) was headed 'New Xyzal'. The leavepiece stated that Zirtek had been refined and the price reduced. This was followed by a series of bullet points, an illustration of a tiger and the strapline 'Refined with power'.

1 Claim 'Xyzal gives a higher response rate than loratadine in allergic rhinitis'

COMPLAINT

Schering-Plough alleged that the claim 'Xyzal gives a higher response than loratadine in allergic rhinitis' breached Clauses 7.2, 7.3 and 8.1 of the Code.

The referenced study, Horak *et al* (2001), related to a cohort of 39 volunteers exposed to allergen in a Vienna Challenge Chamber. These were individuals with only perennial allergic rhinitis. The claim suggested that the study had results in all forms of allergic rhinitis including, for example, seasonal allergic rhinitis. Clearly this was not so.

Schering-Plough was unable to find where the abstract stated that Xyzal had a higher response rate than loratadine. Although there appeared to be a numerical difference between the two products, statistical analysis confirming that the difference was statistically significant was lacking. On request to UCB, it initially received the reply that '… *although Horak did not quote a statistical comparison between Xyzal and loratadine. I believe the difference is statistically significant compared to placebo'*. In further response, UCB had agreed to amend the claim. Schering-Plough stated that it had no evidence that this had been done. In light of UCB's statement in its final response that *'the balance of comparative evidence therefore points to the overall superiority of levocetirizine*

over loratadine' Schering-Plough was not hopeful that any such amendment would be any more accurate.

RESPONSE

UCB stated that the supportive data for the claim came from the Vienna Challenge Chamber. This was a controlled environment, in which patients were exposed to a consistent concentration of a known allergen. This was done to overcome the difficulties of clinical studies, which tended to have variable responses. This view was supported by the high placebo response rates seen in allergic rhinitis studies. It was postulated that one of the reasons for this variability was the environmental variation in allergen concentrations and therefore patient exposure. The controlled environment of allergen challenge chambers was generally accepted as representative of the clinical situation.

Horak *et al* included patients with perennial allergic rhinitis who happened also to be volunteers. In the study, the response rate with Xyzal (83%) was indeed numerically higher than loratadine (66%), which represented a relative increase of 26% in the number of responders with Xyzal compared with loratadine. The statistical significance of the difference between Xyzal and placebo ($p<0.002$) was 10-fold greater than the difference between loratadine and placebo ($p<0.02$), although Horak did not quote a statistical comparison between Xyzal and loratadine. UCB believed the difference was statistically significant compared to placebo and the numerically greater response rate with Xyzal supported the claim.

The claim was further supported by a subsequent Vienna Challenge Chamber study (Horak, data on file) which included 73 patients with seasonal allergic rhinitis. This was a randomised, double-blind, placebo-controlled, 3 periods crossover study, over 2 consecutive days. The author concluded that the efficacy of levocetirizine 5mg in alleviating the symptoms of seasonal allergic rhinitis was shown to be statistically significantly superior to the efficacy of loratadine 10mg over the time interval 1. This superiority was also demonstrated over the subsequent time intervals 2, 3 and 4. Horak did not specifically analyse the results in terms of response rates, looking at the response rates in detail it could be seen that the proportion of patients with a greater than 20% improvement in symptom score was 90% for levocetirizine, 79% for loratadine and 42% for placebo. This compared favourably with the results from the perennial rhinitis study, in which the response rates were 83% for levocetirizine, 66% for loratadine and 43% for placebo.

UCB believed that the obvious numerical difference seen in the perennial allergic rhinitis study and the statistical superiority displayed in the seasonal allergic rhinitis study supported the claim and therefore it was neither misleading nor unsubstantiated.

UCB had no intention of disparaging loratadine but the body of evidence demonstrated superiority of cetirizine over loratadine and there was a developing body of evidence showing the likelihood that this would also be true of levocetirizine.

PANEL RULING

The Panel noted that the Horak *et al* (2001) study had 39 subjects diagnosed as having perennial allergic rhinitis. UCB did not dispute Schering-Plough's view that the subjects were volunteers. The results were that 83.8% of levocetirizine subjects, 66.7% of loratadine subjects and 43.2% of placebo subjects had at least 20% improvement in complex symptom score. The study concluded that both products gave significant control of allergic symptoms caused by exposure to house dust mites under controlled conditions and suggested a faster onset of action of levocetirizine. There was no statistical analysis of the differences between loratadine and levocetirizine. Both products were statistically significantly different to placebo.

The Panel noted the Horak data on file looked at 73 subjects in relation to seasonal allergic rhinitis. Levocetirizine was shown to be statistically superior to loratadine over the time interval. This superiority was more pronounced after the second administration of the medicines.

The Panel noted that Schering-Plough had misquoted the claim which referred to response rate rather than response.

The Panel considered that the claim on the leavepiece was a broad claim which was misleading. The data did show a difference between the products but the difference had not been supported by the statistics with regard to perennial allergic rhinitis. There was no clinical data. The comparison was misleading. Breaches of Clauses 7.2 and 7.3 of the Code were ruled. The Panel considered that the claim disparaged loratadine and a breach of Clause 8.1 was also ruled.

2 Claim 'The new cetirizine'

The claim appeared beneath the brand logo and non-proprietary name.

COMPLAINT

Schering-Plough stated that levocetirizine was one element of the racemic mixture that was cetirizine. It was surely inaccurate to suggest that levocetirizine was a 'new' cetirizine. A new medicine developed from Zirtek, perhaps, but surely not 'the new cetirizine'. Schering-Plough alleged a breach of the supplementary information to Clause 7.10.

RESPONSE

UCB stated that this raised the issue as to whether a recently introduced compound, even when it was identical in molecular formula, structure and had been proven via the regulatory process to be equivalent could use prefixes to suggest a new version of the old compound.

There had been a significant precedent for the use of terms implying newness in this class of treatments. It was relevant that the prefix 'Neo', as used in Schering-Plough's product NeoClarityn, which even though derived from the Greek term *'neos'*, meant

new or reformed. While levocetirizine was identical in structure and formula to cetirizine the same was not true for desloratadine and loratadine; nevertheless the regulatory authorities accepted the trademark NeoClarityn.

As stated cetirizine was a racemic mixture and as such comprised an R-enantiomer and an S-enantiomer. The R-enantiomer was the active form, levocetirizine. Both of these enantiomers had exactly the same molecular formula and chemical structure, although mirror images of each other, and were therefore structurally the same as cetirizine.

The differences arose at a chemical level in the crystals' effect on polarised light. Cetirizine did not rotate polarised light; dextrocetirizine rotated polarised light to the right while levocetirizine rotated polarised light to the left. This became relevant as dextrocetirizine was inactive and the effectiveness of cetirizine arose from levocetirizine. It was therefore neither inaccurate nor inappropriate to state that levocetirizine was essentially a form of cetirizine. UCB submitted that it was not inappropriate to use the word 'new'. The Oxford Dictionary defined many options for new, which included 'renewed or reformed' and 'different from a previous one'. There was no doubt that levocetirizine fulfilled both of these criteria.

Furthermore, at a clinical level there were significant parallels between cetirizine and levocetirizine. As part of the regulatory process an equivalence study was conducted which demonstrated the clinical equivalence of Xyzal 5mg to Zirtek 10mg. There were also significant similarities between the two compounds in as much as cetirizine had a demonstrated effect on nasal congestion, which was also present with levocetirizine.

UCB submitted that subtle or even distinct differences did not preclude the use of terms implying 'newness' in relation to an identical or closely related existing pharmaceutical product, as was the case for NeoClarityn.

UCB believed that the use of the term 'The new cetirizine' fitted within this precedent and was therefore not in breach of Clause 7.10 of the Code.

PANEL RULING

The Panel noted that levocetirizine was one of the constituent parts of cetirizine which was a racemic mixture. The Panel did not consider that the claim was exaggerated or all embracing. It did not imply a special merit that could not be substantiated. The Panel ruled no breach of Clause 7.10 of the Code.

3 Claim 'Xyzal inherits the established safety profile of Zirtek'

COMPLAINT

Schering-Plough did not agree with the rationale for this claim. While levocetirizine was an enantiomer of the racemic mixture of cetirizine, Xyzal remained a different medicine from Zirtek with, for example, the replacement of the excipient maize starch with colloidal anhydrous silica.

Schering-Plough alleged that it was inaccurate for a new medicine, with a black triangle, without the years of pharmacovigilance data Zirtek had, different in at least one constitutive element from Zirtek to attempt to don the mantle of Zirtek's safety profile. Schering-Plough alleged breaches of Clauses 7.2, 7.9 and 7.10 of the Code.

RESPONSE

UCB stated that it had hoped that its response previously to Schering-Plough would have reassured it as to this claim. On the surface UCB accepted that there was a potential issue but closer analysis of the data supported the claim.

UCB submitted that the claim did not breach Clauses 7.9 and 7.10 because the body of evidence supported the similar safety profiles for the two compounds.

Sections 4.8 of the respective SPCs stated 'There have been occasional reports of mild and transient side effects such as headaches, dizziness, drowsiness, agitation, dry mouth and gastrointestinal discomfort' for Zirtek and 'Ninety-five % of these adverse drug reactions were mild to moderate' for Xyzal. Both of these statements suggested that these adverse drug reactions, even though recorded, were not perceived to be injurious or harmful to the patient. This lack of perceived harm with Xyzal was also supported by the subsequent paragraph, which reported the observed drop out rate from the trials. 'In therapeutic trials with levocetirizine, drop out rate for adverse drug reaction under levocetirizine 5mg represented 0.7% (4/538) of the patients, of the same magnitude of what was observed under placebo (0.8%, 3/382)'. This demonstrated a comparable withdrawal rate between Xyzal and placebo.

Examining the types of undesirable effects also suggested marked similarity between the two products. The main side effects experienced by patients fell into the same categories and tended to be related to somnolence, headache, dry mouth and gastrointestinal discomfort. This was further supported by the Global Analysis of Safety (Section 3.3) of the Expert Report on the Clinical Documentation, for levocetirizine dihydrochloride. This concluded:

'The adverse events profile of 5mg levocetirizine is comparable in nature and incidences to those of 10mg cetirizine.

The long post-marketing experience with cetirizine justifies that human exposure to levocetirizine in clinical trials is reduced, particularly in terms of long-term exposure. Indeed, levocetirizine has already been administered chronically, together with the other enantiomer, billions of times, without revealing a safety concern'.

UCB also submitted that the safety of a product was more broadly based than the adverse event profile. There were multiple other statements relating to safety within the Xyzal SPC that referred to previous experience with cetirizine. These were in important areas such as interactions with other substances, experience of use in pregnancy and objective assessment of psychomotor effects on performance.

The Xyzal SPC included the following statements, which extrapolated from this experience with cetirizine: it has been shown that the racemate cetirizine does not potentiate the effect of alcohol; studies with the racemate compound cetirizine demonstrated that there were no clinically relevant adverse interactions; data on a limited number of exposed pregnancies indicate no adverse effects of cetirizine on pregnancy or on health of fetus/new born child and, comparative clinical trials have revealed no evidence that cetirizine, the racemate of levocetirizine, impairs mental alertness, reactivity or the ability to drive. This also applies to the use of this drug in the recommended dosage. UCB submitted therefore that within the SPC many of the key statements relating to the safety profile of Xyzal had been based on the post-marketing experience with cetirizine. Furthermore, both products had a very similar pharmacological profile and therefore new safety issues were unlikely to arise due to pharmacokinetic or pharmacodynamic differences.

With regard to the substitution of maize starch with colloidal anhydrous silica and Schering-Plough's view that this might cause a significant safety concern, UCB submitted that this was unlikely and had not shown itself to be a significant concern in preliminary trials.

On balance, as levocetirizine had been administered as part of the racemate, cetirizine, for 15 years, had a comparable adverse event profile according to the Clinical Expert Report, and that there were multiple references to cetirizine in the SPC then this supported the claim.

PANEL RULING

The Panel noted that Xyzal was subject to special reporting in relation to adverse reactions; this was what was meant by the inverted black triangle symbol. The Panel noted UCB's submission regarding the similarities between the SPCs for Zirtek and Xyzal and Zirtek's established safety profile. The Panel considered nevertheless that the claim was misleading. Despite the similarities between the products it was not yet known whether Xyzal would inherit the established safety profile of Zirtek. The Panel considered that the claim was not capable of substantiation by clinical experience and exaggerated as alleged. The Panel ruled breaches of Clause 7.2, 7.9 and 7.10.

4 Strapline 'Refined with power'

This appeared in capital letters at the foot of the first page.

COMPLAINT

Schering-Plough stated that the first bullet point on this page '…potent purified isomer' was linked with the strapline 'Refined with power' by a series of clinical claims. This linkage gave rise to the impression that the *in vitro* potency was in some way related to these clinical claims.

As there was no clinical data to suggest that Xyzal was more clinically powerful, i.e. more effective than Zirtek, this strapline was alleged to be misleading in breach of Clause 7.2.

RESPONSE

UCB stated that it was generally accepted that the production and promotion of an isolated active isomer was a refinement, hence the term 'Improved Chemical Entity (ICE)', which had used to describe such developments. UCB did not understand why Schering-Plough believed that this strapline linked to any other claim on the leavepiece. The strapline 'Refined with power' was describing Xyzal and was not linked with any of the other claims. Indeed, looking at the positioning on the leavepiece of the first bullet point and the strapline, they were separated by three subsequent bullet points.

There was no suggestion within the material that levocetirizine had more power than cetirizine, which had a large body of evidence to demonstrate power in the treatment of allergic conditions. There was a significant battery of supportive data that levocetirizine was at least as potent as cetirizine at half the dose, as stated in the SPC.

Even if this linkage was true it would not be designed to mislead prescribers as to the clinical relevance of such claims. Stating that Xyzal had a higher potency for the H1 receptor was relevant in the clinical situation, as it explained why the same effect as Zirtek 10mg could be expected from a reduced dose, namely Xyzal 5mg.

PANEL RULING

The Panel considered that the claim implied that Xyzal was more clinically powerful than Zirtek. There was no data in this regard. The dose had been reduced from 10mg Zirtek to 5mg Xyzal. This did not necessarily mean that Xyzal had more clinical power than Zirtek. The Panel noted the supplementary information to Clause 7.2 of the Code that claims for superior potency in relation to weight were generally meaningless and best avoided unless they could be linked to some practical advantage. The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

B Announcement from 'e-news' of doctorsworld.com

The item in question was, according to Schering-Plough, sent as a mailing to all subscribers of doctorsworld.com on 3 October.

1 Claim 'Clinical studies have shown that Xyzal is at least as effective as Zirtek, as well as being effective in relieving nasal congestion'

COMPLAINT

Schering-Plough stated that this was clearly a clinical claim which would be expected to be supported by a clinical study. In requesting support for the claim, Schering-Plough was sent a paper in which the pharmacodynamic properties of levocetirizine in 18 healthy volunteers were reported.

Schering-Plough could not accept that this pharmacodynamic study would suffice to support the claim and a breach of Clause 7.2 was alleged. Attention was drawn to the supplementary information regarding the use of data derived from *in vitro* studies, studies in healthy volunteers and animals.

RESPONSE

UCB stated it had tried to reassure Schering-Plough that the regulatory process for the Xyzal marketing authorization required the equivalence between Xyzal 5mg and Zirtek 10mg to be proven. As previously stated to Schering-Plough:

'The equivalence of Xyzal and Zirtek has certainly been established in seasonal allergic rhinitis in a regulatory phase III trial, involving 797 patients.

This is data on file but I am pleased to enclose the Clinical Study Report for this phase III Regulatory trial, for your consideration.

We will amend this news release and future press releases to state:

A large comparative clinical study has shown that Xyzal 5mg is as effective as Zirtek 10mg in relieving the symptoms of seasonal allergic rhinitis, and a placebo controlled study has shown that Xyzal gives highly significant improvement in the troublesome symptom of nasal congestion associated with perennial allergic rhinitis.'

UCB stated that it would have sent further details of this study had it been requested to do so.

The Medicines Control Agency (MCA) and the other regulatory bodies throughout the European Union had accepted the evidence behind this claim. Pharmacodynamic studies, which also concluded that Xyzal 5mg was at least as effective as Zirtek 10mg, were also supportive of this claim.

PANEL RULING

The Panel noted that the claim was referenced to a study by Potter *et al* (data on file) a placebo-controlled double-blind study on levocetirizine 5mg in 368 patients for the treatment of perennial allergic rhinitis. The study report stated that a statistically significant improvement in the individual symptom scores, particularly in nasal congestion, was observed.

The Panel noted Schering-Plough had referred to an *in vitro* study being sent. This was not commented on by UCB which had provided some clinical data in relation to nasal congestion associated with perennial allergic rhinitis. There appeared to be no clinical data for nasal congestion associated with seasonal allergic rhinitis. The data did not support the claim.

The Panel considered that the claim implied that Xyzal was highly effect in relieving nasal congestion in both seasonal as well as perennial allergic rhinitis. This had not been demonstrated. The claim did not reflect the evidence and a breach of Clause 7.2 was ruled.

2 Claim 'Comparative studies have shown a higher clinical response rate than Clarityn … in allergic rhinitis, and a more pronounced and longer lasting inhibition of histamine mediated wheal and flare skin reactions than both Clarityn 10mg and Telfast …'

The comparison with Clarityn in allergic rhinitis was referenced to Horak *et al* (2001). The comparison of wheal and flare skin reactions was referenced to Grant *et al* (submitted for publication).

COMPLAINT

Schering-Plough alleged that including an *in vitro* study in the midst of clinical claims implied that this finding had some clinical relevance. A breach of Clause 7.2 was alleged.

RESPONSE

UCB stated that it did not understand Schering-Plough's persistence in referring to this as an *in vitro* study. As emphasised this was an *in vivo*, albeit healthy volunteers, pharmacodynamic study. The claim clearly defined this as using histamine induced wheal and flare skin reactions, which were a generally accepted model to compare the relative effectiveness of antihistamines. There was no assertion that this implied that it was clinically relevant, but the author did conclude that the findings of the study 'may predict the efficacy of this drug in treating allergic disorders'.

There was a growing body of wheal and flare data that suggested these findings including trials by Clough *et al* (2001) and Hindmarch *et al* (2001) who both used this model to compare the relative peripheral potency of levocetirizine and loratadine.

PANEL RULING

The Panel noted that the first part of the claim was a clinical claim and the second part claim was referenced to a study by Grant *et al*. The study had been carried out on 18 men with no known allergies. The Panel considered that the claim implied that there was clinical data showing an advantage for Xyzal with regard to wheal and flare skin reactions over 24 hours. This was not so. The basis for this part of the claim had not been made sufficiently clear. The claim was misleading in this regard and the Panel ruled a breach of Clause 7.2 of the Code.

3 Claim 'There is no evidence that Xyzal impairs mental alertness, reaction times or the ability to drive'

COMPLAINT

Schering-Plough alleged that it was surely an exaggeration to state there was 'no evidence'. The SPC stated that 'comparative clinical trials have revealed no evidence' which was not quite the same thing.

One piece of conflicting evidence to the claim was in the Xyzal SPC which stated 'Slightly sedating adverse

reactions such as somnolence, fatigue and asthenia were altogether more common (10.2%) than after placebo (4.4%)'.

The claim was alleged to be exaggerated in breach of Clause 7.10.

RESPONSE

UCB stated that sedation was one of the most troublesome undesirable effects that had been experienced over the years with antihistamines. This was exemplified in an extensive review by Shamsi and Hindmarch (2000) which stated that 'There are two aspects to sedation. The first, an objectively determined measure based on the results of psychometric tests from controlled clinical trials, and the second, the subject's response to the administration of a drug. Since antihistamines are largely used in ambulant patients, a complete evaluation of sedation should be performed through standardised objective and subjective tests shown to be sensitive to the central effects of AHs'.

The evidence for the claim was from the SPC, which stated 'Comparative clinical studies have revealed no evidence that cetirizine, the racemate of levocetirizine, impairs mental alertness, reactivity or the ability to drive. This also applies to the use of this drug in the recommended dosage'.

There were also two controlled trials by Gandon (2001) and Hindmarch (2001), designed to investigate the sedative properties of Xyzal. These both reached the conclusion that there was no impairment of objectively assessed psychomotor function with Xyzal when compared to placebo. UCB accepted that from the pivotal clinical trials the subjective feelings of somnolence were higher for Xyzal than placebo, but there was no evidence that this would lead to mental impairment, reactivity times or the ability to drive.

PANEL RULING

The Panel noted that the Xyzal SPC stated that comparative clinical trials had revealed no evidence that Xyzal impaired mental alertness, reactivity or the ability to drive; it also stated that slightly sedating adverse reactions such as somnolence, fatigue and asthenia were altogether more common (10.2%) than after placebo (4.4%). The Panel considered that the claim at issue did not put the objective measurements of sedation, ie how a patient reacted, into context with the subjective measurements, ie how a patient felt. In this regard the Panel considered that the claim was misleading. A breach of Clause 7.2 of the Code was ruled.

4 Prescribing information

COMPLAINT

Schering-Plough stated that the mailing did not contain prescribing information; a breach of Clause 4.6 was alleged.

RESPONSE

UCB stated that the prescribing information was supplied to the agency representing UCB for inclusion in this Internet statement. It was unfortunate that this was not included but UCB sought to amend this mistake made by the agency as soon as it was made aware of it.

PANEL RULING

The Panel considered that the article was an advertisement and a clear prominent statement as to where the prescribing information could be found should have been included. The Panel ruled a breach of Clause 4.6 as alleged.

5 Claim 'Comparative studies have shown a higher clinical response rate than Clarityn in allergic rhinitis'

COMPLAINT

Schering-Plough alleged that the claim was inaccurate on at least three counts. Firstly, the use of the word 'studies' implied that a number of studies had all reached the same conclusion. In fact there was only one study. Secondly, the study was a volunteer study in 39 individuals with perennial allergic rhinitis exposed to allergen in a Vienna Challenge Chamber. The use of the word 'clinical' implied this was a more real life setting than a volunteer study. Thirdly, the use of 'allergic rhinitis' implied that the results related to all forms of allergic rhinitis, including seasonal allergic rhinitis, when only volunteers with perennial allergic rhinitis, a discrete disease, were tested.

Schering-Plough alleged the claim was in breach of Clauses 7.2, 7.3 and 7.4.

RESPONSE

UCB stated that this was essentially the same as point A1 and referred to its response to that point. The two Vienna Challenge Chamber studies supported the claim. These encompassed both perennial and seasonal allergic rhinitis and UCB believed that the balance of evidence demonstrated the superiority of Xyzal over Clarityn.

UCB stated that for reasons already discussed it was generally accepted that results seen within this environment represented the clinical situation and were a valid method of assessing the therapeutic effect of antihistamines. Furthermore as already described these volunteers were patients, sensitised to the allergen used and whilst in the chamber were definitely suffering from allergic rhinitis. They were therefore representative of allergic rhinitis sufferers even though they chose to volunteer for such trials.

PANEL RULING

The Panel considered that its ruling in point A1 above also applied to the claim now at issue. Breaches of Clauses 7.2 and 7.3 were ruled. Schering-Plough had also alleged that the claim was in breach of Clause 7.4. This had not been alleged in point A1. The Panel ruled a breach of Clause 7.4 as the claim was not capable of substantiation.

C Detail Aid UCB XYZ-01-02

This was a 12 page loose leaf detail aid. Each page bore prescribing information. The different pages of the detail aid were distinguished from one another by the use of a suffix A, B, C etc added on to the reference number.

1 Claim 'Xyzal only contains the levocetirizine enantiomer'

The claim appeared at the bottom of a page (ref UCB-XYZ-01-02B).

COMPLAINT

Schering-Plough alleged that the claim was inaccurate as Xyzal did not only contain levocetirizine; it contained excipients. Informing the medical community of this was particularly important in light of the comment in Section 4.4 of the SPC which stated: 'patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine'. Presumably this warning derived from the small amount of lactose present as an excepient. A breach of Clause 7.2 was alleged.

RESPONSE

UCB stated it had made clear in its reply to Schering-Plough that when removed from the context of the page there was a potential for misunderstanding. However, when adopting the wider view and looking at the page as a whole there was a clear build up to that final bullet point.

This demonstrated the major difference between Zirtek and Xyzal, which was the refinement of the racemic mixture to include just the active enantiomer.

UCB submitted that the claim was not misleading as health professionals had a good understanding that marketed products contained inactive ingredients.

PANEL RULING

The Panel considered that health professionals would not be misled by the claim. Medicines would be expected to include ingredients other than the active ingredient. No breach of Clause 7.2 was ruled.

2 Claim 'High rate of responders in Allergic Rhinitis'

This claim appeared as the heading to a page (ref UCB-XYZ-01-02D). It had been misquoted by Schering-Plough in its complaint as 'High rate of response in Allergic Rhinitis'. The claim was referenced to Horak *et al* (2001).

The page in question included a graph headed 'Clinically relevant improvement in complex nasal symptoms score' which showed that 83.8% of patients taking Xyzal 5mg showed at least a 20% improvement over baseline, the figure for loratadine was 66.6% and placebo 43.3%. Both Xyzal and loratadine were statistically significantly different from placebo ($p< 0.002$ and $p< 0.02$ respectively). The graph in the study was headed 'Percentage of subjects with at least 20% improvement in complex symptom score n=35'.

COMPLAINT

Schering-Plough stated that this claim was again referenced to the study in 39 volunteers with perennial rhinitis exposed to house dust mite antigen in the Vienna Challenge Chamber. This study had no relation to other forms of allergic rhinitis such as seasonal allergic rhinitis. To suggest that approximately 85% of patients, with any kind of allergic rhinitis, would respond to Xyzal was inaccurate and breaches of Clauses 7.2 and 7.10 were alleged.

RESPONSE

UCB stated that again this study was referenced to the Vienna Challenge Chamber study investigating the effects in perennial allergic rhinitis. This study did reflect that in this controlled environment 85% of the patients achieved a pre-determined clinically relevant response, defined as a 20% improvement in the complex symptom score. UCB believed that this response rate of 85% represented a high rate of response. The subsequent study in the same environment including 73 seasonal allergic rhinitis patients showed an even higher rate of responders at 90%.

Adding these data to the pivotal studies, consisting of the dose ranging study which demonstrated superiority over placebo, for Xyzal 2.5mg and the equivalence study, showed the overall effectiveness of Xyzal. This effectiveness had been undeniably demonstrated in both seasonal and perennial allergic rhinitis and was supportive of the claim at issue.

PANEL RULING

The Panel noted that Schering-Plough had misquoted the claim. The Panel considered that the Horak study (2001) and the Horak data on file showed a high rate of responders in perennial and seasonal allergic rhinitis respectively. The page was only referenced to Horak *et al* (2001) and not also to the Horak data on file. The Panel did not consider that the claim was misleading or exaggerated and ruled no breach of Clauses 7.2 and 7.10 of the Code.

3 Claim 'Faster than loratadine at relieving nasal symptoms'

The claim appeared beneath the graph on the same page as at issue in point C2 above. It was also referenced to Horak *et al* (2001).

COMPLAINT

Schering-Plough alleged that this claim was also based on the same study in 39 volunteers in the Vienna Challenge Chamber. The conclusion of the report was 'This study … suggests a faster onset of action of levocetirizine' [emphasis added]. No statistical comparison of the time of onset of levocetirizine against loratadine was made. A breach of Clause 7.2 was alleged.

In addition the claim appeared to suggest that Xyzal was faster at relieving nasal symptoms in all conditions including, for example, seasonal allergic rhinitis. As no evidence was put forward for this all embracing claim Schering-Plough alleged breaches of Clauses 7.2, 7.3 and 7.4 of the Code.

RESPONSE

UCB stated that the claim was clearly explained by the subsequent bullet point 'Unlike loratadine Xyzal showed significant response 1 hour after dosing'. From the referenced poster Xyzal had a statistically significant improvement over placebo at 1 hour with a p value <0.005. At this time loratadine was not significantly different from placebo and indeed needed until to 2 hours post administration to achieve this same level of significance. UCB had however agreed to change the claim.

PANEL RULING

The Panel noted that the Horak *et al* 2001 data concluded that the study suggested a faster onset of action of levocetirizine compared to loratadine. The main criteria for efficacy was the complex symptom score which was the total score for rhinorrhoea, itching of the nose and sneezing. The Panel referred to its comments in point A1 above.

Horak *et al* data on file evaluated efficacy using the major symptoms score (MSC) which related to scores for runny nose, itchy nose, sneezing, watery eyes and itchy eyes. The study also evaluated MSC plus nasal obstruction which showed a significant superiority of levocetirizine over loratadine in time intervals 1, 3 and 4. The Panel queried these data as it appeared there was no separate assessment of nasal symptoms.

The Panel noted that the claim was referenced to a study on 39 subjects diagnosed with perennial allergic rhinitis. There was no data with regard to nasal symptoms for seasonal allergic rhinitis. The comparison in the study in question was between loratadine and placebo and levocetirizine and placebo. There was no comparison between levocetirizine and loratadine. The Panel considered that the claim was not fair, it was a misleading comparison and was not capable of substantiation. The Panel ruled breaches of Clauses 7.2, 7.3 and 7.4 of the Code.

4 Claims 'Highly predictable response' and 'Xyzal displays low intersubject variability'

The claims appeared on a page (ref: UCB-XYZ-01-02F) headed 'Highly predictable response' which detailed the results of Grant *et al* (2001). The heading was qualified by use of an asterisk to the statement 'inhibition of histamine - induced skin reactions'. These were followed by a graph comparing areas under the curve (AUC) - Flare area (0-24h) for Xyzal, fexofenadine, loratadine and placebo. The graph was followed by a claim 'Xyzal was significantly superior to loratadine, and fexofenadine (180mg) in reducing wheal and flare'. The second claim at issue 'Xyzal displays low intersubject variability' appeared as the next bullet point.

COMPLAINT

Schering-Plough noted that these claims were referenced to a study by Grant *et al* (2001) which was a study on 18 'healthy male volunteers'. Nowhere in the leavepiece was this study population mentioned. This gave the impression of a medicine with predictable pharmacokinetics over a whole spectrum of patients when it had only been tested in a highly homogenous volunteer population, a population that was therefore likely to have a low intersubject variability. Schering-Plough alleged that this claim was in breach of Clause 7.2, especially in reference to the supplementary information to this clause related to the use of data from volunteer studies.

RESPONSE

UCB stated that these were important considerations in the treatment of any conditions where individual response to treatment could affect the outcome and hence satisfaction of the treatment. The histamine induced wheal and flare response was an accepted and validated method of objectively assessing the response to treatment.

The study by Grant demonstrated the very predictable response with Xyzal. UCB accepted that this study was conducted in a relatively homogenous population in as much as they were male and healthy. There was however a diverse age range from 18-54 years. The pharmacokinetic profile of Xyzal had been shown to be predictable with no differences being seen between genders. UCB perceived that this was a wide enough age range to suggest a heterogeneous population being exposed to this effect. Furthermore, the trial was conducted as a crossover design. This meant that all of the products tested would have had the same opportunity to demonstrate such an effect, within this same population.

This predictable effect in a wheal and flare model was further supported by data from Clough. The study by Clough, which again involved relatively low numbers in a crossover design, demonstrated that 4 hours after intake all patients who received Xyzal obtained statistically greater responses than placebo or loratadine. This was also true of the sensation of histamine-induced itch, which was subjectively assessed. Consideration of the data for loratadine revealed a very variable response that in some subjects was no greater than placebo.

The data from the Vienna Challenge Chamber study by Horak also demonstrated the high response rate, as previously discussed.

The data confirmed the highly consistent and predictable effect suggested by Grant. This was seen in a heterogeneous population which included healthy volunteers subjected to histamine challenges, as well as patients exposed to allergen in the Challenge Chamber.

PANEL RULING

The Panel noted that the page did not make it clear that the data was obtained from 18 healthy male volunteers aged 18 - 54. The Panel noted that Xyzal

was licensed for children aged 6 - 12 years as well as adolescents and adults. The data referred to did not cover the entire patient population. The Panel considered that the claims at issue were misleading as alleged and ruled each in breach of Clause 7.2 of the Code.

5 Claim 'More effective than Zirtek'

This claim appeared as a heading to a page (ref UCB-XYZ-01-02G). It was followed by an asterisk which gave the explanation 'inhibition of histamine-induced skin reaction'. The page featured a graph showing the percentage inhibition of wheal against time post-dose for cetirizine (5mg) and levocetirizine (2.5mg). The difference between the products was statistically significant ($p<0.02$) in favour of levocetirizine. The page was referenced to a study by Devalia *et al* (2001).

COMPLAINT

Schering-Plough alleged that without qualification readers were likely to consider this claim to mean that Xyzal was more clinically effective than Zirtek. However the only data produced was for histamine-induced skin reaction. This model was of extremely doubtful significance in chronic idiopathic urticaria, and was of no relevance in perennial or seasonal allergic rhinitis. The claim implied a clinical effect from pre-clinical data. The supplementary information to Clause 7.2 suggested that such extrapolation of data should only be made where there was data 'to show that it is of direct relevance and significance'. There was none such here and Schering-Plough alleged a breach of Clause 7.2.

RESPONSE

UCB stated that the claim was clearly qualified by the asterisked bullet point 'inhibition of histamine-induced skin reaction'. There was no attempt to imply a clinical effect.

In this situation it was designed to prove the principle that by removing the inactive enantiomer there were pharmacodynamic differences between Xyzal and Zirtek. Cetirizine showed good activity in various pharmacodynamic studies in both the nose and skin and was often chosen as the comparator molecule for assessing the activity of a new treatment. As such this claim was of direct relevance to prescribers as UCB wished to assure them that Xyzal was at least equipotent to Zirtek at 50% of the dose, as stated in the SPC.

However, contrary to Schering-Plough's view the histamine-induced wheal and flare was a validated and internationally accepted method for detecting differences between antihistamines. It had been widely utilised over many years.

The ability of the H_1 antagonist to inhibit the histamine-induced wheal and flare reaction was a well documented technique and probably the most reliable method for assessing their histamine antagonistic activity in humans, comparing either their relative potency or their time of onset and duration of action.

UCB therefore believed that the use of such pharmacodynamic data was recognised by the body of opinion as relevant in the comparison of the H_1 antagonistic effects of products marketed as antihistamines. UCB therefore believed that the use of such models should be acceptable within the Code.

PANEL RULING

The Panel noted that the Devalia *et al* (2001) study was carried out on 18 male healthy volunteers aged 18-41 years. None of the volunteers were skin prick test positive to any of the common allergens. All demonstrated a histamine-induced mean skin wheal diameter of >8mm by skin prick test. With the exception of AUC inhibition of wheal there were no significant differences in percentage of maximum inhibition, time of maximum inhibition, onset time, end time and duration of inhibition of the wheal or flare for the two compounds. The study concluded that levocetirizine 2.5mg had comparable antihistaminic activity to cetirizine 5mg. The doses were not the licensed doses for the products.

The Panel considered that the implication was that clinically Xyzal was more effective than Zirtek. There was no data to support such a claim. The Panel ruled a breach of Clause 7.2 of the Code.

6 Claim 'In objective tests of psychomotor function, the incidence of sedation with Xyzal was similar to placebo'

The claim appeared on a page (ref UCB-XYZ-01-02I) headed 'Excellent safety profile – prescribe with confidence' followed by a subheading 'No impairment of daily activities'.

COMPLAINT

Schering-Plough alleged that the claim was at variance to Section 4.8 of the Xyzal SPC which stated 'Slightly sedating adverse reactions such as somnolence, fatigue, and asthenia were thus altogether more common (10.2%) [after Xyzal] than after placebo (4.4%)'. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

UCB stated that as it had tried to clarify in its reply to the Schering-Plough, this clearly related to objective assessment and as such was not at variance with Section 4.7 of the SPC which dealt with the objective ability to perform specific tasks like driving.

As already described, Section 4.7 of the SPC stated: 'Comparative clinical trials have revealed no evidence that cetirizine, the racemate of levocetirizine, impairs mental alertness, reactivity or the ability to drive. This also applied to the use of this drug in the recommended dosage'.

UCB had already discussed the difficulty surrounding the definition of sedation. Hindmarch clearly stated that there were two aspects to sedation. The objective assessment of psychomotor impairment using psychometric tests in a controlled environment was

one aspect and the subjective feeling of somnolence, as reported as a secondary aim within clinical trials was the second. There was also a growing body of data as to the non-impairing effects of Xyzal, as was demonstrated by the poster presented by Gandon, and the recently published paper by Hindmarch. These were both on the objective assessment of sedation compared to placebo.

UCB accepted that in Section 4.8 of the SPC that there were higher figures for subjective symptoms such as somnolence, but UCB submitted that as Section 4.8 did not relate to the objective assessment of sedation that it was not relevant in this instance.

PANEL RULING

The Panel noted its ruling in point B3 above. The Panel considered that the claim did not reflect all the evidence: the results of subjective tests of sedation had not been stated. In this regard the Panel noted Section 4.8 of the Xyzal SPC. The claim was misleading as alleged The Panel ruled a breach of Clause 7.2 of the Code.

7 Claim 'No impairment of daily activities'

This claim appeared as a subheading on the page at issue at C6 above. It was followed by two bullet points 'In objective tests of psychomotor function, the incidence of sedation with Xyzal was similar to that of placebo' the claim at issue in C6 and 'Zyzal does not impair mental alertness, reactivity or the ability to drive.

COMPLAINT

Schering-Plough stated that it could not find, nor could UCB supply, any data related to a clinical trial examining any measurement of 'daily activity' except for the ability to drive.

Schering-Plough had asked UCB if there were any data to suggest that, with the exception of the ability to drive, the sedative potential of Xyzal described in the SPC did not impair daily activities, and received the following response '… evidence can be extrapolated to **most** [emphasis added] daily activities that require performance skill, not just driving'.

Schering-Plough alleged that the claim suggested that UCB was aware that this all-embracing claim could not be supported and perhaps UCB even agreed with Schering-Plough's contention that this was in breach of Clause 7.10.

RESPONSE

UCB stated that there was no evidence and no statement in the SPC that suggested that the incidence of subjective reports of somnolence, fatigue or asthenia, even though more common than placebo, led to any impairment of daily activities.

However Section 4.7 clearly stated that Xyzal did not impair mental alertness, reactivity or the ability to drive, at the recommended dose. The regulatory authorities had accepted these data. They were based on a battery of psychometric tests, which investigated central processing, sensorimotor performance and sensory and motor skills and could be extrapolated to daily activities.

PANEL RULING

The Panel noted its rulings in point C6 and B3 above. The claim did not reflect the statements in the SPC. The Panel considered that the claim was all embracing as alleged and a breach of Clause 7.10 of the Code was ruled.

D Xyzal Condensed Product Summary UCB – XYZ-01-01B

This was an 18 page booklet. The section in question was on page 11. The page referred to studies by Devalier *et al* (2001) (point C6) Grant *et al* (2001) (point C5) and Clough *et al* (2001) (point C8). The results from Clough were shown in detail.

Section on 'Chronic Idiopathic Urticaria'

COMPLAINT

Schering-Plough alleged that throughout this whole section much was made of the use of the histamine-induced wheal and flare as 'a surrogate endpoint for urticarial lesions'. Schering-Plough stated that the text stated that 'levocetirizine was statistically superior to loratadine for wheal and flare response' and mentioned the 'high potency and predictability of levocetirizine in inhibiting wheal and flare reactions compared to mizolastine, fexofenadine, loratadine and ebastine'. The prominence given to pre-clinical data appeared designed to suggest a clinical difference in activity between Xyzal and other antihistamines.

The histamine-induced wheal and flare was not a valid surrogate endpoint for urticarial lesions. A review entitled 'Appraisal of the validity of histamine-induced wheal and flare to predict the clinical efficacy of antihistamines' clearly described the flaws of using histamine-induced wheal and flare as a predictive tool for the efficacy of antihistamines (Monroe *et al* 1997). Two quotes from this review helped to demonstrate the controversy around the use of this model.

'Although the histamine-induced wheal and flare reaction can serve as a useful clinical pharmacologic test to assess dose-response relations for an antihistamine, **its lack of correlation with clinical responses among antihistamines indicates that this model should not be used to predict or compare clinical efficacies of antihistamines in seasonal allergic rhinitis and chronic idiopathic urticaria'** [emphasis added].

The reason for this was that 'the allergic responses in these tissues are not simply the consequence of one chemical but are the result of a cascade of interactions among various cells and mediators. The clinical manifestations of these complex interactions obviously cannot be fully replicated by injection of one chemical mediator, histamine, into the outer layer of the skin'.

Schering-Plough stated that two-thirds of the page on chronic idiopathic urticaria related to the effect of levocetirizine on histamine-induced wheal and flare. This prominence and the lack of any attempt to put the uncertainties as to the clinical relevance of this test into context were alleged to be in breach of Clauses 7.2 and 7.3 of the Code.

RESPONSE

UCB noted that Schering-Plough raised the same issue regarding the usefulness of the histamine-induced wheal and flare reaction and that UCB had already offered its view regarding this. There were experts within the field of allergy who were prepared to accept that this model might predict the usefulness of this model in predicting the clinical effect of a medicine. Grant in his poster presented at the European Academy of Allergology and Clinical Immunology meeting this year made such an assertion. UCB accepted that there was this view which was why it chose the expression that it used carefully. The direct quote from the page in question was '…a histamine- induced wheal and flare could be considered as a surrogate endpoint…'. Even Schering-Plough accepted that this fact remained controversial and therefore the use of the term 'could be considered' was accepting of this degree of disagreement.

Furthermore, UCB would suggest that comparative wheal and flare data between cetirizine and loratadine had largely been predictive of the clinical effect seen in therapeutic studies. Studies conducted in the Environmental Exposure Unit, Ontario, in addition to a large outdoor study demonstrated the statistical superiority of cetirizine over loratadine in seasonal allergic rhinitis. The wheal and flare studies comparing levocetirizine and loratadine were also predictive of the results that were being demonstrated within the Vienna Challenge Chamber.

UCB stated that even though it accepted that the allergic mechanism in chronic idiopathic urticaria and perennial allergic rhinitis involved mediators other than histamine the established view was that antihistamines worked predominately by blocking the effect of histamine at the histamine receptor.

There was also a developing opinion that any additional activity, for example anti-inflammatory action, was a product of antihistamine potency which could be reliably assessed by using the wheal and flare response. The pharmacodynamic data would certainly suggest that cetirizine and now levocetirizine were among the more potent antagonists of the H_1 receptor and this might explain why to date they were the only antihistamines to demonstrate anti-inflammatory properties *in vivo* at the recommended therapeutic dose.

UCB believed that there was sufficient evidence to support the use of the wheal and flare method in predicting the potential use of an antihistamine, where the effect was occurring in a peripheral tissue. This would then support the claim suggesting that it could be used as a surrogate endpoint for the urticarial lesion.

PANEL RULING

The Panel noted that the page was devoted to the view that a histamine-induced wheal and flare could be considered as a surrogate endpoint for urticarial lesions. The data was all on human volunteers. Clough *et al*, a study on 11 healthy male volunteers, concluded that levocetirizine was a potent inhibitor of the effects of histamine in human skin with an efficacy that exceeded that of loratadine 10mg when single doses were administered four hours before the test.

The Panel considered that the applicability of the wheal and flare test in volunteers with no history of allergy to the treatment of patients with chronic idiopathic urticaria was not as clear cut as implied by UCB. The data was more limited than the impression given. It was not immediately clear that the results shown did not relate to patients. The laser-doppler images shown implied that Xyzal 5mg would be more effective in treating chronic idiopathic urticaria than Zirtek 10mg. There was no clinical data to support this. The Panel considered that in this regard the page was misleading. Breaches of Clauses 7.2 and 7.3 were ruled.

Complaint received **6 December 2001**

Case completed **1 March 2002**

CASE AUTH/1265/12/01

GENERAL PRACTITIONER v NOVARTIS

Failure to position the non-proprietary name correctly

A general practitioner complained that a Starlix brochure, sent to him by Novartis, was in breach of the Code because although the non-proprietary name, nateglinide, appeared as part of the brand logo on the back page, it was not immediately adjacent to the most prominent display of the brand name as required.

The Panel decided that the most prominent display of the brand name was that which appeared on an inside page of the brochure; this was the mention that readers would notice first. As the non-proprietary name did not appear immediately adjacent to it the Panel ruled a breach of the Code.

COMPLAINT

A general practitioner complained about the promotion of Starlix by Novartis Pharmaceuticals UK Limited. The material at issue was a mailing to general practitioners and practice nurses with a special interest in diabetes. The mailing consisted of a 'Dear Doctor' letter and a brochure.

The complainant pointed out that the 'Dear Doctor' letter contained both the trade name 'Starlix' and the approved name 'nateglinide' in their recommended arrangement. The four page brochure did not refer to Starlix on its front cover but there were several mentions of the brand name on pages 2 and 3; the non-proprietary name, nateglinide, appeared as part of the brand logo on the back page. The complainant alleged that the brochure did not comply with the requirement for the approved name to be displayed immediately adjacent to the most prominent display of the brand name.

RESPONSE

Novartis acknowledged that the complainant had correctly noted that the non-proprietary name had been appropriately included on the 'Dear Doctor' letter and also on the back of the brochure but not adjacent to the first use of the brand name on the brochure.

Novartis accepted that each item must comply in its own right; however, the brochure in question formed an integral part of the complete mailing and would not have been sent to health professionals without the accompanying letter. The accompanying letter, as acknowledged by the complainant, included the appropriately positioned non-proprietary name as specified in the supplementary information to Clause 4.3.

The omission of the non-proprietary name on the brochure immediately adjacent to the first use of the brand name was an oversight and Novartis stated that it would not argue which use of the brand name on this item would represent the most prominent. In view of the complaint the brochure had been withdrawn and would not be used again.

PANEL RULING

The Panel noted that Clause 4.3 of the Code required that the non-proprietary name/list of active ingredients appeared immediately adjacent to the most prominent display of the brand name in bold type of a size such that a lower case 'x' was no less that 2mm in height or in type of such a size that it occupied a total area of no less than that taken up by the brand name. The most prominent display of a brand name was that which first caught readers' attention; it was not necessarily the first use of the brand name as inferred by Novartis.

The Panel noted that the brochure contained several references to the brand name 'Starlix'. The issue to be decided was which was the most prominent display. The Panel decided that the most prominent display of the Starlix brand name was that which appeared in logo type at the bottom right hand corner of page three of the mailing. This was the mention of the brand name that readers would notice first. Failure to include the non-proprietary name immediately adjacent to this display of the brand name meant that Novartis had failed to meet the requirements of Clause 4.3 and a breach of that clause was ruled.

Complaint received	**14 December 2001**
Case completed	**6 February 2002**

PARAGRAPH 17 v IVAX (NORTON)

Cactus prescribing service

A document entitled 'Cactus practice effective prescribing', concerning a Norton Healthcare (now known as Ivax) service, was the subject of complaint in Case AUTH/1155/3/01. No breach of the Code was ruled.

On receipt of a report on the case, in accordance with Paragraph 4.1 of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority, the Code of Practice Appeal Board was concerned that the Ivax system support specialists might not be appropriately qualified people to have access to confidential patient information and so the Cactus prescribing system might fail to meet the requirements of the Code. The Appeal Board requested that, in accordance with Paragraph 17.1 of the Constitution and Procedure, the matter be taken up with the company.

In Case AUTH/1155/3/01, the Panel had noted that the Cactus system was offered in association with the promotion of medicines both by medical representatives and in promotional material, and decided that it was therefore subject to the Code.

Guidance given in the November 1999 issue of the Code of Practice Review on the provision of medical and educational goods and services stated, *inter alia*, 'Only an appropriately qualified person, for example a sponsored nurse, not employed as a medical/generic representative, may undertake activities relating to patient contact and/or patient identification'. The same wording now appeared in the supplementary information in the 2001 edition of the Code.

The system support specialists had access to data which identified patients. Ivax submitted that these were appropriately qualified persons because they had appropriate experience and training in practice management, computing systems and administration. The Panel considered that, given the role undertaken by the system support specialists, there was considerable merit in this argument. If an 'appropriately qualified person' had to be a health professional of some sort, then the guidance should have stated that fact. A 'sponsored nurse' was given only as an example. The Panel noted that access to confidential medical information was not limited to health professionals. Administrative staff in practices and hospitals who had relevant responsibilities also had access to such information. The position of the system support specialists in this respect was admittedly arguable but, on balance, the Panel considered that they were 'appropriately qualified persons' as specified in the 1999 guidance and the supplementary information in the 2001 Code.

The guidance and the new supplementary information also stated that 'Neither the company nor its medical/generic representatives may be given access to data/records that could identify, or could be linked to, particular patients'. The Panel noted that it had been established in Case AUTH/1155/3/01 that the system support specialists were not representatives as defined in the Code and Ivax had submitted that the confidential patient details were not taken out of the practice. Neither Ivax itself nor its medical/generic representatives thus had access to the confidential information.

Taking these factors together, the Panel considered that there had been no breach of the Code in relation to the system support specialists accessing confidential information and ruled accordingly.

The Panel noted that the reference under Paragraph 17 had related solely to the question of access by the system support specialists to confidential information.

A document entitled 'Cactus practice effective prescribing' (ref CT PSD [BKLT 12.98]), concerning a Norton Healthcare Limited service, was the subject of complaint in Case AUTH/1155/3/01. No breach of the Code was ruled. Norton had since changed its name to Ivax Pharmaceuticals UK Limited.

COMPLAINT

When the Code of Practice Appeal Board received a report on the case in accordance with Paragraph 4.1 of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority, it expressed concern that the Baker Norton system support specialists might not be appropriately qualified people to have access to confidential patient information and so the Cactus prescribing system might fail to meet the requirements of Clause 18.1 of the Code. The November 1999 Code of Practice Review published guidance on the provision of medical and educational goods and services under Clause 18.1 of the Code which stated, *inter alia*, that only an appropriately qualified person, for example a sponsored registered nurse, not employed as a medical/generic representative, might undertake activities relating to patient contact and/or patient identification. Neither the company nor its medical/generic representatives might be given access to data/records that could identify, or could be linked to, particular patients.

The Appeal Board noted Norton Healthcare's submission that at no stage were patient medical details accessed but considered that patient identities must have been available. Clause 18 of the Code was not cited by the complainant in Case AUTH/1155/3/01 and therefore its provisions were not considered by the Panel in relation to the case. The Appeal Board requested that, in accordance with Paragraph 17.1 of the Constitution and Procedure, the matter be taken up with Norton Healthcare.

RESPONSE

Ivax noted that in relation to the published guidance, the Code of Practice Panel had accepted in Case AUTH/1155/3/01 that the Ivax System Support Specialists (ISSSs) did not act or represent themselves as medical/generic representatives. Notwithstanding, Ivax recognised the legitimate questions as to the

extent to which the service provided came within the 'provision of medical and educational goods and services' and it was under this that their activities were being considered in relation to Clause 18.1.

Equally, whereas the role of the ISSS was clearly not that of a medical/generic representative, nor was it that of a sponsored health professional, for example a nurse. No component or element of the service offered might be reasonably construed as 'medical' to the extent that no medical advice or clinical views were given.

To this extent therefore, Ivax found the Code and associated guidance silent, in that it did not address the question of service provision which was neither promotional nor medical in nature. In this case the ISSSs were acting in a manner identical to the non-medically qualified practice staff themselves, who in their daily activities were involved in data processing. The services provided were controlled by the general practitioner who was acting as 'data controller'. Only the minimum data set necessary to fulfil the task was accessed, which did not extend to the patient's medical records in terms of history, diagnoses or other notes. The minimum data did include the patient's name and address for patients on a particular medication.

It was inevitable that in the total care provision for any patient within the NHS, numerous auxiliary and support staff required access to certain information in order to provide their service. Access to and processing of certain patient information by staff other than those medically qualified was not inappropriate or improper *per se*. Further, in the same regard Ivax believed the Data Protection Act directed that access be by a qualified medical professional or someone who had the same duty of confidentiality. Similarly the General Medical Council advised that such activities were carried out by someone who was appropriately trained to carry out the task. Ivax did not see in these circumstances, or feel there should be, any distinction between the ISSSs by virtue of their employment by Ivax, as opposed to their employment by the NHS or indeed any other third party. The Authority might be aware there were a number of independent companies currently providing similar services on behalf of UK based pharmaceutical companies.

The essence of the role was to provide appropriate computer and administrative support to medical practices that had requested such support. Hence the role requirement was for staff with appropriate experience and training in the areas of practice management, computing systems and administration. Typically this included knowledge of the computer based prescribing system in use as well as the key principles of practice management. Indeed Ivax's current team of five ISSSs was all drawn from this background, ie they had the proven experience and career history that would be required of practice management and administration staff with whom they worked in concert. Ivax had in the past also employed nursing staff, although the qualifications had not been a requirement of the position, and had not been utilised in any way in the provision of the service.

The ISSS entered a practice, on request, only following receipt of the Cactus document, signed by two GPs, one of whom was required to be a/the senior partner, and also the practice manager. Typically a mutually convenient appointment was thus agreed at which point a company Healthcare Specialist would accompany the ISSS to facilitate the appropriate introductions to practice staff. The Healthcare Specialist would then leave the premises. The ISSS at all times carried and displayed a photo-identity badge and initiated proceedings by volunteering (if not requested) to sign the practice confidentiality agreement where such existed. At this point the previously described elements of the Cactus document and procedure were reviewed with the responsible practice manager or GP, who then granted the necessary authority for the ISSS to access the minimum data sets from computer records.

The search process then identified those patients on the previously agreed medicines. The ISSS would then proceed with any amendments required as authorised by the appropriate partner's signature for each and every revision on the Cactus document.

No records were removed or taken from the practice database, except for the number of switches agreed. Any switch or revision was endorsed by the responsible GP. The necessary communication between the practice and the patient was by letter, the content and issue of which was under the practice control and responsibility, although the ISSS might assist in their preparation.

Ivax hoped that these comments clarified the ISSS role, which was a support service providing data processing administrative computer support to the practice. Their qualifications to supply such a service lay in their background, training in computer related administrative roles and accepted duty of confidentiality which mirrored that of the practice staff. At all times a clear separation and distinction was maintained from Ivax promotional activities.

Ivax concluded this information should sufficiently address the Appeal Board's concerns as to a possible breach of Clause 18.1.

PANEL RULING

The Panel noted that confidential data, the names and addresses of patients on a particular medicine, was accessed by the ISSSs, although this information was not taken away from the practice by them.

In Case AUTH/1155/3/01, the Panel had noted that the Cactus system was offered in association with the promotion of Norton's medicines both by medical representatives and in promotional material, and decided that it was therefore subject to the Code. As the Cactus system was subject to the Code, it followed from that that all activities which it involved, and all personnel who carried out those activities, were subject to the Code. The ISSSs were thus subject to the Code even though they did not themselves promote medicines.

Turning to the present case, the point to be decided was whether it was acceptable for the ISSSs to access the names and addresses of patients on particular

medicines in relation to the requirements of Clause 18.1.

The guidance given in the November 1999 issue of the Code of Practice Review stated, *inter alia*, 'Only an appropriately qualified person, for example a sponsored nurse, not employed as a medical/generic representative, may undertake activities relating to patient contact and/or patient identification'. The same wording now appeared in the supplementary information to Clause 18.1 in the 2001 edition of the Code.

The ISSSs clearly had access to data which identified patients. Ivax argued that the ISSSs were appropriately qualified persons because they had appropriate experience and training in practice management, computing systems and administration. The Panel considered that, given the role undertaken by the ISSSs, there was considerable merit in this argument. If an 'appropriately qualified person' had to be a health professional of some sort, then the guidance should have stated that fact. A 'sponsored nurse' was given only as an example. The Panel noted that access to confidential medical information was not limited to health professionals. Administrative staff in practices and hospitals who had relevant responsibilities also had access to such information. The position of the ISSSs in this respect was admittedly arguable but, on balance, the Panel considered that they were 'appropriately qualified persons' as specified in the 1999 guidance and the supplementary information in the 2001 Code.

The guidance and the new supplementary information also stated that 'Neither the company nor its medical/generic representatives may be given access to data/records that could identify, or could be linked to, particular patients'. The Panel noted that it had been established in Case AUTH/1155/3/01 that the ISSSs were not representatives as defined in Clause 1.6 of the Code and Ivax had submitted that the confidential patient details were not taken out of the practice. Neither Ivax itself nor its medical/generic representatives thus had access to the confidential information.

Taking these factors together, the Panel considered that there had been no breach of Clause 18.1 in relation to the ISSSs accessing confidential information and ruled accordingly.

The Panel noted that the reference under Paragraph 17 had related solely to the question of access by the ISSSs to confidential information. It had not therefore been required to examine the Cactus system in relation to the new supplementary information to Clause 18.1 as a whole. Ivax should be advised to examine all aspects of the Cactus system in the light of the new supplementary information to check that it was compliant with the Code.

Proceedings commenced 15 November 2001

Case completed 17 December 2001

CASE AUTH/1268/12/01

BRISTOL-MYERS SQUIBB and SANOFI-SYNTHELABO v NOVARTIS

Diovan detail aid

Bristol-Myers Squibb and Sanofi-Synthelabo complained jointly about a GP detail aid for Diovan (valsartan) issued by Novartis.

The page in question was headed 'Working hard where there's risk' followed by a sub-heading 'Why choose DIOVAN for patients with type 2 diabetes?'. Two subsequent bullet points read 'DIOVAN has been shown to provide a significant reduction in microalbuminuria over a year' and 'Microalbuminuria is a predictor of premature mortality in patients with diabetes'. A graph depicted the percentage reduction in microalbuminuria from baseline following therapy with captopril (–27%), placebo (+18%) and Diovan 80mg (-28%). Beneath the graph was a third bullet point 'DIOVAN is significantly more effective than amlodipine in reducing microalbuminuria'.

The complainants pointed out that Diovan was only licensed for the treatment of essential hypertension and alleged that the claims in the detail aid for reductions in albumin excretion in patients with type 2 diabetes meant that Novartis was promoting Diovan for a use outside of its marketing authorization and encouraging its representatives to do the same.

The Panel noted that the claim regarding the reduction in microalbuminuria was referenced to Muirhead *et al* (1999) in which patients were either normotensive or treated hypertensives but all with type 2 diabetes mellitus and microalbuminuria. Before commencing the study the majority of patients allocated to receive Diovan had not received antihypertensive treatment.

The Panel considered that the page advocated use of Diovan for patients with type 2 diabetes. There was no mention on the page of hypertension. The Panel noted that captopril, which was shown in the graph on the same page to reduce microalbuminuria by 27%, was licensed for the treatment of hypertension as well as being separately indicated for the treatment of diabetic nephropathy in insulin-dependent diabetics. The Panel considered that the page was inconsistent with the marketing authorization for Diovan and a breach of the Code was ruled.

The Panel did not consider it necessary to make a separate ruling about the representatives. The allegation was covered by its ruling above.

Bristol-Myers Squibb Pharmaceuticals Limited and Sanofi-Synthelabo Limited complained jointly about a GP detail aid (ref DI0 01/51) for Diovan (valsartan) issued by Novartis Pharmaceuticals UK Ltd. Valsartan was an angiotensin II receptor antagonist (AII antagonist).

Page 6 of the detail aid was headed 'Working hard where there's risk' followed by a sub-heading 'Why choose DIOVAN for patients with type 2 diabetes?'. Two subsequent bullet points read 'DIOVAN has been shown to provide a significant reduction in microalbuminuria over a year' and 'Microalbuminuria is a predictor of premature mortality in patients with diabetes'. A graph depicted the percentage reduction in microalbuminuria from baseline following therapy with captopril (–27%), placebo (+18%) and Diovan 80mg (–28%). Beneath the graph was a third bullet point 'DIOVAN is significantly more effective than amlodipine in reducing microalbuminuria'.

COMPLAINT

Bristol-Myers Squibb and Sanofi-Synthelabo stated that they had expressed concerns to Novartis about the sub-heading and two bullet points which referred to the use of Diovan in patients with type 2 diabetes. Diovan was only licensed for the treatment of essential hypertension. The complainants, therefore, alleged that the claims for reductions in albumin excretion in patients with type 2 diabetes represented the promotion of Diovan for a use outside of its marketing authorization.

The complainants also maintained that by making the claims about reduction in microalbuminuria within the detail aid, Novartis was encouraging its representatives to proactively promote Diovan for a use outside of its licensed indication.

Breaches of Clause 3.2 of the Code were alleged.

RESPONSE

Novartis stated that microalbuminuria occurred in between 5% and 40% of hypertensive patients and was therefore not an infrequent finding in this patient group (Rosa *et al* 2000). Microalbuminuria occurring in hypertensive patients was associated with an increased risk of cardiovascular events (Campese *et al* 2000).

Hypertensive patients with type 2 diabetes were at an increased risk of cardiovascular disease compared to the 'general' hypertensive population (UK Prospective Diabetes Study Group 1998). Current national guidelines (British Hypertension Society 1999) recommended that the subgroup of hypertensive patients with diabetes should have their blood pressures reduced more aggressively than non-diabetic hypertensive patients as this further reduced morbidity and mortality.

Studies had demonstrated that a reduction in blood pressure in hypertensive patients with type 2 diabetes reduced microalbuminuria. As this had been achieved with agents from various antihypertensive classes it had been concluded that the simple haemodynamic effect of reducing blood pressure reduced microalbuminuria (Maki *et al* 1995).

The different classes of antihypertensive medicines reduced blood pressure by different mechanisms. ACE inhibitors and AII antagonists, which reduced blood pressure by acting on the renin-angiotensin system, had been repeatedly shown to reduce microalbuminuria to a greater extent than other classes. It had been suggested that this was due to their specific mode of action which, in contrast to other antihypertensives, also reduced blood pressure locally within the kidney.

It should also be noted that for some time now companies marketing the most widely prescribed AII antagonists, including the complainants, had been interpreting their licences in respect of hypertension in a similar fashion to Novartis. This had been demonstrated by the inclusion in their materials of references to the reduction in microalbuminuria when treating hypertensive patients who also suffered from type 2 diabetes.

In summary, microalbuminuria was commonly found in hypertensive patients in which it indicated an increased cardiovascular risk. The subgroup of hypertensives with type 2 diabetes could reduce their high cardiovascular risk by aggressive antihypertensive treatment. Reducing blood pressure in hypertensives with type 2 diabetes tended to reduce microalbuminuria. However, ACE inhibitors and AII antagonists reduced this to a greater extent as a result of their specific blood pressure lowering mechanisms. In addition, Novartis submitted that the reference to microalbuminuria included in the detail aid was consistent with statements for other medicines in the class.

Accordingly, Novartis did not accept the complainants' suggestion that a reference to the reduction of microalbuminuria during therapy with Diovan represented a breach of Clause 3.2 of the Code.

PANEL RULING

The Panel did not consider that Novartis' comments about the marketing of medicines by other companies were relevant to its consideration of this case. Each case was considered on its own merits.

The Panel noted that the claim regarding the reduction in microalbuminuria was referenced to Muirhead *et al* (1999) which was carried out on 122 normotensive and treated hypertensive patients with type 2 diabetes mellitus and microalbuminuria. It was a multicentre, randomized, double-blind, placebo and captopril controlled, parallel-group trial to evaluate the efficacy and safety of valsartan 80 and 160mg in patients with incipient diabetic nephropathy. Patients were randomized to receive either valsartan 80mg or 160mg once daily, captopril 25mg 3 times daily, or placebo. Efficacy variables included albumin excretion rate (AER), progression to clinical proteinuria, and glomerular filtration rate. In both the valsartan 80mg (n=31) and 160mg (n=31) groups and in the captopril group (n=29), a decrease in AER from baseline was observed at end point, compared with an increase in the placebo group (n=31). The positive effect of valsartan 80mg versus placebo on AER was statistically significant (95% confidence interval (CI) for end point/baseline ratio: 0.365 to 0.966); the 95% CI for valsartan 160mg versus placebo was 0.406 to 1.043. No significant differences in AER occurred in the comparisons of valsartan 80mg and valsartan 160mg versus captopril. The authors stated that the results suggested that treatment with valsartan slowed the progressive rise in AER in normotensive and treated hypertensive patients with type 2 diabetes mellitus with comparable efficacy and superior tolerability to captopril.

The Panel noted that Diovan was licensed only for the treatment of hypertension. Not all the patients in the Muirhead study had hypertension. Before commencing the study 21 (67.7%) of patients allocated valsartan 80mg treatment and 22 (71%) of patients allocated valsartan 160mg had not received antihypertensive treatment. The majority of the patients, 75 out of 122, had not received treatment for hypertension. It might be that the patients were undiagnosed hypertensives. The Panel noted that national guidelines on the treatment of hypertension recommended that the threshold for initiating antihypertensive therapy in a patient who also had diabetes should be lower than that in a patient who did not have diabetes. The definition of hypertension would thus differ in the two groups. However, the study clearly referred to part of the population as being normotensive.

The Panel considered that the page of the detail aid in question advocated use of Diovan for patients with type 2 diabetes. There was no mention at all on the page of hypertension. The Panel noted that captopril, which was shown in the graph on the same page to reduce microalbuminuria by 27%, was licensed for the treatment of hypertension as well as being separately indicated for the treatment of diabetic nephropathy in insulin-dependent diabetics. The Panel considered that the page was inconsistent with the marketing authorization for Diovan; it was not clear that for patients to be eligible for Diovan treatment they had to be hypertensive and a breach of Clause 3.2 of the Code was ruled.

The Panel did not consider that it was necessary to make a separate ruling about the representatives. The allegation was covered by its ruling about the section of the detail aid in question.

During its consideration of this case the Panel considered that it was arguable whether it was appropriate to use the results from a study whereby only 39% of the patients had been using antihypertensive medication in promotional material for a antihypertensive medicine. The Panel also noted that the representative's briefing material referred to Diovan 80mg as 'the most ideal choice …'. The Panel considered that the use of the superlative 'most' did not relate to a clear fact about Diovan as required by Clause 7.10 of the Code. The Panel requested that its concerns be drawn to the attention of the company.

Complaint received **20 December 2001**

Case completed **18 February 2002**

CASE AUTH/1269/1/02

FOREST LABORATORIES v CHIRON CORPORATION

Promotion of Tobi

Forest Laboratories complained about the promotion of Tobi (tobramycin) by Chiron Corporation. Tobi was presented as a solution for nebulisation for the long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in cystic fibrosis (CF) patients aged 6 years and older. Forest marketed Colomycin Injection (colistin) which could be administered via a nebuliser.

The claim 'Tobi represents a significant advance over current treatments for patients chronically colonised with *Pseudomonas aeruginosa*' was the opening sentence of the Economic Support Document for Tobi in Cystic Fibrosis. Forest alleged that the claim was misleading as whilst it might be true for the US where inhaled antibiotic therapy was seldom used and relatively unsophisticated, in the UK Tobi represented no more than an alternative to inhaled Colomycin. In addition it implied that Tobi was an advance over all treatments for patients chronically colonised with *P. aeruginosa*.

The Panel noted Chiron's submission that it did not intend to imply that Tobi was an advance over all treatments for patients chronically colonised with *P. aeruginosa*. Chiron was only comparing Tobi to standard care in the US and to another nebulised antibiotic used in the UK. There was no data directly comparing Tobi with inhaled Colomycin. Tobi was only licensed for the long-term management of chronic pulmonary infection due to *P. aeruginosa* in CF patients aged 6 years and older. Although the title of the document referred to the use of Tobi in cystic fibrosis, the Panel nonetheless considered that the specific patient group for which Tobi was licensed should have been stated in the first sentence. To not make it clear at the outset to which patient group the claim referred was misleading. It appeared that any patient chronically colonised with *P. aeruginosa* could be treated with Tobi which was a significant advance over current treatments. In the Panel's view this was not so. Breaches of the Code were ruled.

In relation to the claim '…[modern treatments like Tobi] can often demonstrate health economic benefits that may represent significant savings on current management approaches', Forest stated that there was no evidence that Tobi represented significant savings in the UK on current management approaches. Similarly the statement 'often demonstrate health economic benefits' was an unsupported generalisation. The Panel noted that the paragraph in which the claim appeared opened with 'Tobi represents a significant advance…' (considered above). The Panel considered that the whole paragraph would be assumed to apply to Tobi and not just to 'modern treatments'. Any claims made for modern treatments would be assumed also to apply to Tobi. With respect to Tobi the Panel considered that the claims made were misleading and not capable of substantiation. No material had been supplied to substantiate the claims in relation to savings with Tobi. Breaches of the Code were ruled.

The booklet referred to a US study by Ramsey *et al* (1999) in which treatment with Tobi was compared to placebo in CF patients with *P. aeruginosa* infection who were also receiving standard care. Forest noted that 'standard care/therapy' was not defined and therefore its use was misleading. Standard care of CF patients in the US prior to the introduction of Tobi was not the same as in the UK as there was no general use of inhaled antibiotic, even access to physiotherapy (a crucial part of lung clearance) differed. Any comparison with care in the US was accordingly extremely misleading. As a general principle the Panel noted that before making clinical claims based on overseas studies companies should satisfy themselves that, *inter alia*, the study was relevant to current UK practice. Similarly before making claims about the economic benefits of a medicine, based on such data, the company should be sure that the study was relevant to current UK prices. The booklet in question was an economic support document for Tobi. In the Panel's view readers would assume that all the claims made in the booklet were relevant to UK practice and prices. The Panel considered that by not explaining what was meant by standard care/therapy the booklet was misleading. Readers could not put the results of Ramsey *et al* into context; they did not know how, or if, standard care/therapy in the US differed from standard care/therapy in the UK. A breach of the Code was ruled. The Panel considered that the term 'standard care/therapy' could be capable of substantiation even though in the booklet it had not been defined. No breach of the Code was ruled in that respect.

Forest noted that the claim 'Reduced use of IV antibiotics' appeared in a section of the booklet based on a study based on 'standard' US treatment (ie patients not receiving nebulised antibiotic treatment) versus patients with Tobi. Since there were no circumstances in the UK where a CF patient colonised with *P. aeruginosa* would not be considered for active therapy, the comparisons were misleading. The Panel noted the general principle set out in a ruling above. The Panel considered that without the information to set the claim into the context of UK practice the comparisons were misleading as alleged. Breaches of the Code were ruled.

A bar chart depicted health outcomes over 24 weeks. There was a 37% reduction in hospitalization in the Tobi group compared with placebo and a 26% reduction in days off work or school due to illness. Forest stated that there was no evidence provided (or referenced) in the booklet that similar benefits would be achieved in the UK. The Panel noted the general principle set out above. Chiron was undertaking a health economic audit to see whether the claims that it had made, based on US data, would apply in the UK. The Panel considered that the claims had not been substantiated as alleged and ruled a breach of the Code.

A subsection entitled 'Selection of patient groups likely to benefit most from Tobi' highlighted in particular adolescents with CF, patients with CF unresponsive or intolerant to other inhaled antibiotics and patients awaiting lung transplants. Forest noted that the first sentence of the subsection read, 'Assuming that data from the North American Studies translate to the UK environment…'. In view of the already stated and highly significant differences in treatment patterns in the UK compared to the US, Forest questioned the basis for this assumption. In addition the lack of substantiation rendered everything that followed misleading and inaccurate. The Panel noted the general principle set out above. The Panel considered that without the information to set the claims into the context of UK practice the information was misleading and could not be substantiated as alleged. From the opening sentence of the subsection it was not clear whether the data did have any relevance to the UK. Breaches of the Code were ruled.

The claim '…savings are likely to be even greater in the case of severely affected patients…' appeared in a subsection entitled 'Selection of patient groups likely to benefit most from Tobi'. Forest noted that patients in the Tobi studies had between 25% - 75% of predicted FEV_1. There was no evidence to support the use of Tobi in severely affected patients. This statement was therefore highly speculative and the company failed to see how greater savings could be claimed when even in the US studies this aspect was not specifically measured. The Panel noted the general principle set out above. The Panel considered that the claim for greater savings in the case of severely affected patients had not been substantiated as alleged. A breach of the Code was ruled.

The claim 'Although there have been no controlled studies in patients awaiting lung transplants, anecdotal evidence suggests that using Tobi in these patients may be a useful adjunctive therapy in maintaining lung function during this period' also appeared in the subsection entitled 'Selection of patient groups likely to benefit from Tobi'. Forest alleged a breach as Chiron had admitted that it did not have supportive clinical data. The Panel noted that there was no clinical evidence with regard to the use of Tobi in CF patients awaiting lung transplantation, only anecdotal reports. In the Panel's view claims could not be based upon such data and such data did not thus constitute substantiation. A breach of the Code was ruled. The Panel did not consider that the claim was exaggerated or all-embracing and no breach of the Code was ruled in that respect.

The claims '… a reduced need for intravenous antibiotics' and 'patients on Tobi are expected to spend more time out of hospital' appeared in a subsection headed 'Possible savings when using Tobi'. Forest alleged that both of these claims were hanging comparisons. Forest also failed to see how replacing existing nebulised antibiotic therapy with Tobi resulted in a reduced need for IV antibiotics. The claim was not referenced and Forest knew of no UK study that supported it. The Panel considered that the two claims were hanging comparisons. It was not clear to what Tobi was being compared and a breach of the Code was ruled. The claim for '… a reduced need for intravenous antibiotics' was based upon the results of Ramsey *et al*. The Panel noted the general principle set out above. It was unclear whether the US study would translate into UK practice. The Panel considered that the claim could not be substantiated as alleged. A breach of the Code was ruled.

The claim 'Thus the annual net cost per patient from Tobi introduction is £1686' appeared as the penultimate bullet point under a heading of 'Summary of likely budget impact on an average Health Authority of introducing Tobi'. Forest alleged that the claim was misleading. The Panel noted the general principle set out above. The Panel considered that the reader did not have enough information about the basis of the US study to know whether to accept or reject the claim with regard to UK clinical practice. The Panel considered the claim was misleading as alleged. A breach of the Code was ruled.

The claim 'After 92 weeks of cyclical treatment with Tobi the mean FEV_1 was 4.7% above pre-treatment baseline' appeared in a Tobi Clinical Summary. The claim was referenced to Nickerson *et al* (1999) and appeared beneath a graph from the same study. The graph also showed data until the 92 week time point. Forest noted that the claim referred to data at the end of an 'active' cycle. No account was taken of the fact that weeks 92 to 96 were in fact 'off therapy'. The summary of product characteristics (SPC) for Tobi required cyclical therapy – 28 days on followed by 28 days off. Week 96 marked the end of the Nickerson study and this was published in the original poster. Data in the poster showed that at week 96 pulmonary function declined to baseline thus suggesting that efficacy was unchanged over the 96 week period. This was contrary to the graph used in the Tobi Clinical Summary which ended at week 92. The Panel noted that the corresponding graph from the original reference showed data up until 96 weeks at which time FEV_1 had returned to baseline values following initial improvement with treatment. The graph in the Clinical Summary only showed data up until 92 weeks and the claim at issue similarly referred to the results at 92 weeks. Ninety two weeks marked the end of an active treatment month although the whole eight week cycle would not be completed until 96 weeks. The Panel considered that both the graph and the claim were misleading as they related to data obtained half way through a treatment cycle. Breaches of the Code were ruled.

Forest Laboratories Europe complained about the promotion of Tobi (tobramycin) by Chiron Corporation Ltd. Tobi was presented as a solution for nebulisation for the long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in cystic fibrosis (CF) patients aged 6 years and older. Forest marketed Colomycin Injection (colistin) which could be administered via a nebuliser.

A Economic Support Document for Tobi in Cystic Fibrosis

Chiron explained that this booklet (ref 00079) had been used by its salesforce to help health professionals prepare cost-economic arguments to help secure funding for Tobi. Following intercompany discussions Chiron informed Forest, on 27 September 2000, that the booklet would be revised. Chiron withdrew the booklet immediately pending revision and it had not been used or distributed in the UK since that date.

1 Claim 'Tobi represents a significant advance over current treatments for patients chronically colonised with *Pseudomonas aeruginosa*'

This was the opening sentence of the 12 page booklet.

COMPLAINT

Forest alleged that the claim was misleading in breach of Clause 7.2. Whilst the claim might be true for the United States where inhaled antibiotic therapy was seldom used and relatively unsophisticated, in the UK Tobi represented no more than an alternative to inhaled Colomycin. In addition the wording implied that Tobi was an advance over all treatments for patients chronically colonised with *P. aeruginosa*, this was a breach of Clause 7.10.

RESPONSE

Chiron considered that Tobi was a significant advance in many ways, namely formulation and validated drug delivery system; evidence based data from large randomised controlled clinical trials; long-term improvements in FEV_1, unmatched by current antibiotics available for inhalation.

Chiron stated that unlike intravenous antibiotic formulations of tobramycin, Tobi had been specifically formulated for inhalation. Formulations for inhalation were substantially different from those intended for oral or intravenous use. A solution specifically designed for inhalation must balance osmolality, pH, saline concentration, and antibiotic concentration to ensure both airway tolerance and efficient nebulisation. Extemporaneous preparations of tobramycin might be variable in these product characteristics and might not conform to the appropriate manufacturing standards for inhaled solutions. In addition Chiron conducted several *in vitro* and clinical studies to identify jet nebuliser and compressor characteristics that could match the desired particle size and deliver an adequate amount of tobramycin to the peripheral airways in order to validate the drug-delivery system.

Chiron stated that it had demonstrated efficacy and tolerability of Tobi in the largest double-blind, randomised study of a nebulised antibiotic in CF patients to date (Ramsey *et al*, 1999). Results showed that Tobi increased lung function (as measured by FEV_1) by an average of 11.9% above baseline ($p<0.001$) at 20 weeks. Tobi was found to be particularly effective in adolescents where the improvement in FEV_1 was 15.9% above baseline ($p<0.001$; 23% treatment effect).

Safety and efficacy data during long-term treatment were gathered during an open label extension to the 24 week studies. A total of 396 patients elected to continue to receive Tobi for up to 96 weeks; these results had recently been reported (Moss, 2001). FEV_1 % predicted was maintained at or above baseline throughout 96 weeks. In addition to the actual FEV_1 improvements achieved, it was recognised that lung function declined at around 2-4% a year in CF patients (Rosenberg, 1992; Ramsey, 1999). This decline could clearly be seen in the group that did not receive Tobi during the 24 week randomised part of the study (Ramsey, 1999). Any treatment that could maintain lung function levels in CF patients at or above pre-treatment baseline for 96 weeks would clearly be considered efficacious.

Chiron stated that it was confident that this magnitude of improvement in lung function had never been demonstrated in a randomised controlled trial of any other nebulised antibiotic used in CF. Taking into consideration this and the other points raised the company maintained that Tobi was a significant advance over current treatments for chronically colonised CF patients.

There was no intention to imply that Tobi was an advance over *all* treatments for patients chronically colonised with *P. aeruginosa*. The rest of the document made it clear that the company was only comparing Tobi to standard care in the US and to another nebulised antibiotic used in the UK. Chiron did not agree that this was a breach of the Code.

PANEL RULING

The Panel noted Chiron's submission that it did not intend to imply that Tobi was an advance over all treatments for patients chronically colonised with *P. aeruginosa*. Chiron was only comparing Tobi to standard care in the US and to another nebulised antibiotic used in the UK. There was no data directly comparing Tobi with inhaled Colomycin.

The Panel noted that Tobi was only licensed for the long-term management of chronic pulmonary infection due to *P. aeruginosa* in cystic fibrosis patients aged 6 years and older. Although the title of the document referred to the use of Tobi in cystic fibrosis the Panel nonetheless considered that the specific patient group for whom Tobi was licensed should have been stated in the first sentence. To not make it clear at the outset to which patient group the claim referred was misleading; it appeared that any patient chronically colonised with *P. aeruginosa* could be treated with Tobi which was a significant advance over current treatments. In the Panel's view this was not so. Breaches of Clauses 7.2 and 7.10 were ruled.

2 Claim '…[modern treatments like Tobi] can often demonstrate health economic benefits that may represent significant savings on current management approaches'

This claim was the last sentence of the first paragraph of the booklet.

COMPLAINT

Forest stated that there was no evidence that Tobi represented significant savings in the UK on current management approaches. Similarly the statement 'often demonstrate health economic benefits' was an unsupported generalisation. Breaches of Clauses 7.2 and 7.4 were alleged.

RESPONSE

Chiron stated that the paragraph in question referred to 'modern treatments' and not to Tobi *per se*. There was also no reference to the UK in this paragraph. Chiron considered that the statement 'they (modern treatments) can often demonstrate health economic benefits and may represent significant savings on current management approaches' could be substantiated if necessary and was therefore not in breach of the Code. One example could be the use of TNF α-inhibitors in severe rheumatoid arthritis reducing hospitalizations and costs associated with joint surgery.

PANEL RULING

The paragraph in question opened with 'Tobi represents a significant advance…' (point 1 above). The Panel considered that the whole paragraph would be assumed to apply to Tobi and not just to 'modern treatments'. Any claims made for modern treatments would be assumed also to apply to Tobi. With respect to Tobi the Panel considered that the claims made were misleading and not capable of substantiation. No material had been supplied to substantiate the claims in relation to savings with Tobi. Breaches of Clauses 7.2 and 7.4 were ruled.

3 Reference to 'Standard care/therapy'

Pages 2 and 3 of the booklet referred to a study by Ramsey *et al* (1999) conducted in the US in which treatment with Tobi was compared to placebo in CF patients with *P. aeruginosa* infection who were also receiving standard care.

COMPLAINT

Forest noted that 'standard care/therapy' was not defined and therefore its use was misleading in breach of Clause 7.2.

Forest stated that standard care of CF patients in the US prior to the introduction of Tobi was not the same as in the UK as there was no general use of inhaled antibiotic, even access to physiotherapy (a crucial part of lung clearance) differed. Any comparison with care in the US was accordingly misleading in the extreme. Forest alleged a breach of Clause 7.4.

RESPONSE

Chiron stated that it had already committed to Forest to add this definition at the next reprint to improve clarity. The company stated that it had clearly acknowledged that it was referring to standard care in the US and therefore did not accept that this was misleading or in breach of the Code.

PANEL RULING

Pages 2 and 3 of the booklet gave details of Ramsey *et al*. As a general principle the Panel noted that before making clinical claims based on overseas studies companies should satisfy themselves that, *inter alia*, the study was relevant to current UK practices. Similarly before making claims about the economic benefits of a medicine, based on such data, the company should be sure that the study was relevant to current UK prices. The booklet in question was an economic support document for Tobi. In the Panel's view readers would assume that all the claims made in the booklet were relevant to UK practice and prices.

The Panel considered that by not explaining what was meant by standard care/therapy the booklet was misleading. Readers could not put the results of the study by Ramsey into context; they did not know how, or if, standard care/therapy in the US differed from standard care/therapy in the UK. A breach of Clause 7.2 was ruled.

Forest had also alleged that the use of the term 'standard care/therapy' could not be substantiated. The Panel considered that the term could be capable of substantiation even though in the booklet it had not been defined. No breach of Clause 7.4 was ruled.

4 Claim 'Reduced use of IV antibiotics'

This claim appeared as a subheading on page 3 of the booklet.

COMPLAINT

Forest noted that this section was based on a study based on 'standard' US treatment (i.e. patients not receiving nebulised antibiotic treatment) versus patients with Tobi. Since there were no circumstances in the UK where a CF patient colonised with *P. aeruginosa* would not be considered for active therapy, the comparisons were misleading, Forest alleged breaches of Clauses 7.2 and 7.3.

RESPONSE

Chiron stated that it had made it clear on pages 2 and 3 that the data and graph referred to on these pages referred to the reduced use of IV antibiotic and reduction in days in hospital seen in the US study and therefore considered that this was not misleading or a breach of the Code.

PANEL RULING

The Panel noted the general principle set out in its ruling in point A3 above. The Panel considered that without the information to set the claim into the context of UK practice the comparisons were misleading as alleged. Breaches of Clauses 7.2 and 7.3 were ruled.

5 Claims for less time in hospital and less days off work/school

A bar chart on page 3 depicted health outcomes over 24 weeks. There was a 37% reduction in

hospitalization in the Tobi group compared with placebo (5.1 days vs 8.1 days respectively; p<0.003) and a 26% reduction in days off work or school due to illness (5.2 days vs 7 days respectively; p<0.05).

COMPLAINT

Forest stated that there was no evidence provided (or referenced) in the booklet that similar reductions in hospitalization or days off work/school would be achieved in the UK. The company submitted that in order to be able to make this claim a study would need to be performed comparing Tobi with conventional existing UK practice. Forest alleged a breach of Clause 7.4.

RESPONSE

Chiron stated that it was presenting a worked example of a model based on US data (which was clearly acknowledged throughout the piece) that the health professional might chose to accept or refute.

Tobi unlike colistin had been shown to improve lung function rather than just to prevent decline (Ramsey *et al*) and it therefore seemed reasonable to conclude that there were likely to be some reductions in the need for supportive care in the UK i.e. hospitalization and use of IV antibiotics for exacerbations. Chiron stated that it was currently undertaking a health economic audit to see whether this was indeed the case.

PANEL RULING

The Panel noted the general principle set out in its ruling in point A3 above. Chiron was undertaking a health economic audit to see whether the claims that it had made, based on US data, would apply in the UK. The Panel considered that the claims had not been substantiated as alleged and ruled a breach of Clause 7.4.

6 Subsection entitled 'Selection of patient groups likely to benefit most from Tobi'

This subsection appeared on page 4 of the booklet and highlighted in particular adolescents with CF, patients with CF unresponsive or intolerant to other inhaled antibiotics and patients awaiting lung transplants.

COMPLAINT

Forest noted that the first sentence of the subsection read, 'Assuming that data from the North American Studies translate to the UK environment…'. In view of the already stated and highly significant differences in treatment patterns in the UK compared to the US, Forest questioned the basis for this assumption (Clause 7.4). In addition the lack of substantiation rendered everything that followed misleading and inaccurate (Clause 7.2).

RESPONSE

Chiron stated that it did not consider that it could be in breach of the Code, as by including the phrase 'Assuming that the data translate to the UK environment…' it was clearly acknowledging that the reader might choose to accept or reject this assumption. The company had openly acknowledged that this economic support argument was based on US data and had presented a worked example of how this might translate to the UK environment. Chiron stated that it also made the model available to health professionals so that they might enter the cost relevant to their hospital, and so derive tailored data if they wished.

PANEL RULING

The Panel noted the general principle set out in its ruling in point A3 above. The Panel considered that without the information to set the claims into the context of UK practice the information was misleading and could not be substantiated as alleged. The opening sentence began 'Assuming that the data from the North American studies translate to the UK environment…'. It was therefore not clear whether the data did have any relevance to the UK. Breaches of Clauses 7.2 and 7.4 were ruled.

7 Claim '…savings are likely to be even greater in the case of severely affected patients…'

This claim appeared in the subsection entitled 'Selection of patient groups likely to benefit most from Tobi'.

COMPLAINT

Forest noted that patients in the Tobi studies had between 25% - 75% of predicted FEV_1. There was no evidence to support the use of Tobi in severely affected patients – this statement was therefore highly speculative and the company failed to see how greater savings could be claimed when even in the US studies this aspect was not specifically measured. Forest alleged a breach of Clause 7.4 of the Code.

RESPONSE

Chiron stated that the Ramsey study included patients with an FEV1 of >25 - <75% predicted. The mean FEV_1 of study patients on entry was 50% and the efficacy results quoted in the paper related to this mean population. Analysis of the subgroup of patients on the study, showed a mean change in FEV_1 compared to placebo of 12% after 12 weeks.

Robson *et al* (1992) showed that there was a higher level of health care utilisation in patients with CF being treated in hospital with intravenous antibiotics, which by definition would be the more severe patients.

PANEL RULING

The Panel noted the general principle set out in its ruling in point A3 above. The Panel considered that the claim for greater savings in the case of severely affected patients had not been substantiated as alleged. A breach of Clause 7.4 was ruled.

8 Claim 'Although there have been no controlled studies in patients awaiting lung transplants, anecdotal evidence suggests that using Tobi in these patients may be a useful adjunctive therapy in maintaining lung function during this period'

This claim also appeared in the subsection entitled 'Selection of patient groups likely to benefit from Tobi'.

COMPLAINT

Forest alleged that this claim was in breach of Clauses 7.4, 7.5 and 7.10 of the Code as Chiron had admitted that it did not have supportive clinical data.

RESPONSE

Chiron stated that it was aware of evidence from several major centres of successful use of Tobi in CF patients awaiting transplantation. The company stated that it had referred clearly to these data being anecdotal and therefore did not see how this could be constructed as misleading. These patients did not represent a new indication but a subset of CF patients chronically colonised with *Pseudomonas*.

PANEL RULING

Clause 7.2 of the Code required that all information, claims or comparisons be based on an up-to-date evaluation of all evidence and reflect that evidence clearly. Clause 7.4 required that all such information claims or comparisons must be capable of substantiation. There was no clinical evidence with regard to the use of Tobi in CF patients awaiting lung transplantation, only anecdotal reports. In the Panel's view claims could not be based upon such data and such data did not thus constitute substantiation. The Panel did not consider that the claim could be substantiated. A breach of Clause 7.4 was ruled. The Panel considered that the allegation of a breach of Clause 7.5, failure to provide substantiation, was covered by this ruling.

Forest had also alleged a breach of Clause 7.10 of the Code but the Panel did not consider that the claim was exaggerated or all-embracing and so no breach of that clause was ruled.

9 Claims '… a reduced need for intravenous antibiotics' and 'patients on Tobi are expected to spend more time out of hospital'

These claims appeared in a subsection headed 'Possible savings when using Tobi'.

COMPLAINT

Forest alleged that both of these claims were hanging comparisons in breach of Clause 7.2.

Forest also failed to see how replacing existing nebulised antibiotic therapy with Tobi resulted in a reduced need for IV antibiotics. The claim was not referenced and Forest knew of no UK study that supported it. A breach of Clause 7.4 was alleged.

RESPONSE

Chiron submitted that it had already committed to Forest to correct the statements at the next reprint to remove the statements that could be considered as hanging comparisons.

Chiron stated that it disagreed with the assertion that there were no references to Tobi resulting in reduced need for IV antibiotics. The large, double-blind randomised US study by Ramsey *et al* clearly showed a reduction in use of IV antibiotics and days of hospitalization with the use of Tobi.

Chiron stated that it was aware that there were no UK studies to support this assertion. This was often the case for the type of health economic data generated during phase III studies (which were often essential for achieving funding in the NHS) where product development had occurred mainly overseas. Chiron reiterated that it was presenting a worked example of a model based on US data. This was clearly acknowledged throughout the piece, and the health professional might chose to accept or refute this. Chiron noted that it was clearly stated on page 6 that 'The exact savings will depend on current practice and patients selected for the use of Tobi', and that the company had clearly outlined all assumptions that had been made.

PANEL RULING

The Panel considered that the two claims were hanging comparisons. It was not clear to what Tobi was being compared such that Tobi therapy reduced the need for IV antibiotics or resulted in patients spending more time out of hospital. A breach of Clause 7.2 was ruled.

The claim for '… a reduced need for intravenous antibiotics' was based upon the results of the American study by Ramsey *et al*. The Panel noted the general principle set out in its ruling in point A3 above. It was unclear whether the US study would translate into UK practice. The Panel considered that the claim could not be substantiated as alleged. A breach of Clause 7.4 was ruled.

10 Claim 'Thus the annual net cost per patient from Tobi introduction is £1686'

This claim appeared on page 6 of the booklet as the penultimate bullet point under a heading of 'Summary of likely budget impact on an average Health Authority of introducing Tobi'.

COMPLAINT

Forest stated that the claim was based on previously claimed and unsupportable statements and assumptions. The company alleged that the claim was misleading in breach of Clause 7.2 of the Code.

RESPONSE

Chiron stated that as it disagreed that the preceding statements referred to were misleading, it also believed that the conclusion was not misleading. The company stated that throughout the piece it had

openly acknowledged that it was presenting a worked illustrative example of how US data might translate to the UK environment. The reader might then choose to accept or reject this argument as relating to their own clinical practice.

PANEL RULING

The Panel noted the general principle set out in its ruling at point A3 above. The Panel considered that the reader did not have enough information about the basis of the US study to know whether to accept or reject the claim with regards to UK clinical practice. The Panel considered the claim was misleading as alleged. A breach of Clause 7.2 was ruled.

B Tobi Clinical Summary

Claim 'After 92 weeks of cyclical treatment with Tobi the mean FEV_1 was 4.7% above pre-treatment baseline'

This claim appeared on page 6 of the Clinical Summary. The claim was referenced to Nickerson *et al* (1999) and appeared beneath a graph from the same study. The graph also showed data until the 92 week time point.

COMPLAINT

Forest noted that the claim referred to data at the end of an 'active' cycle. No account was taken of the fact that weeks 92 to 96 were in fact 'off therapy'. The summary of product characteristics (SPC) for Tobi required cyclical therapy – 28 days on followed by 28 days off. Week 96 marked the end of the Nickerson study and this was published in the original poster. Data in the poster showed that at week 96 pulmonary function declined to baseline thus suggesting that efficacy was unchanged over the 96 week period. This was contrary to the graph used in the Tobi Clinical Summary which ended at week 92. Forest alleged breaches of Clauses 7.2, 7.3 and 7.8.

RESPONSE

Chiron stated that the Clinical Summary was used as a UK monograph for Tobi to provide appropriate health professionals with a précis of the clinical, pharmaceutical and pharmacokinetic information for Tobi. It was sent out by medical information and used by the salesforce with customers.

It was clear from the poster, and the publication by Moss *et al* that superseded it, that the investigators chose to highlight the lung function measurements taken at 20, 44, 68 and 92 weeks (at the end of the 3rd 6th 9th and 12th active cycle respectively) and the company had reproduced these results in its Clinical Summary.

The statement that the 96 week function declined back to baseline suggesting that efficacy was unchanged, showed a lack of understanding of the nature of the natural course of the lung function decline in CF and of the study presented. Lung function declined at around 2-4% a year in CF patients (Rosenberg, 1992; Ramsey, 1999) and this mainly accounted for patients' reduced life expectancy. This decline could clearly be seen in the group (allocated to placebo) that did not receive Tobi during the 24 week randomised part of the study (Ramsey, 1999). Any treatment that could maintain lung function levels in CF patients at or above pre-treatment baseline for 96 weeks would clearly be considered efficacious.

Chiron submitted that with hindsight, it might have been prudent to include the 96 week figure in the graph on page 6 for completeness. The company considered, however, that the measurement at 92 weeks was valid, that it corresponded with the endpoints highlighted in the supporting reference, and that the graph was not in breach of the Code.

PANEL RULING

The Panel noted that the graph from the original reference showed data up until 96 weeks at which time FEV_1 had returned to baseline values following initial improvement with treatment.

Tobi was to be administered in eight week cycles; 28 days of therapy followed by 28 days of no Tobi therapy. The graph in the Clinical Summary only showed data up until 92 weeks and the claim at issue similarly referred to the results at 92 weeks. Ninety two weeks marked the end of an active treatment month although the whole eight week cycle would not be completed until 96 weeks. The Panel considered that both the graph and the claim were misleading as they related to data obtained half way through a treatment cycle. Breaches of Clauses 7.2 and 7.8 were ruled.

Forest had also alleged a breach of Clause 7.3 which related to comparisons of medicines or services. The graph and claim at issue constituted a claim for Tobi not a comparison of it with another medicine. No breach of Clause 7.3 was ruled.

Complaint received **9 January 2002**

Case completed **28 February 2002**

CASE AUTH/1271/1/02

ALLERGAN v PHARMACIA

Xalacom summary of product characteristics

Allergan complained about a Xalacom summary of product characteristics (SPC) issued by Pharmacia. Xalacom was an eye drop solution containing latanoprost and timolol. Pharmacia also marketed eye drops containing only latanoprost (Xalatan).

The dark blue front cover of the SPC was headed 'New Xalacom'; the word 'new' was boxed and the letter X of Xalacom was in a logo form. Below the product name were the non-proprietary names and below these in turn was 'Summary of Product Characteristics'. The front cover also featured a representation of the components of Xalacom ie Xalatan, latanoprost (depicted as an electrical plug), and timolol (depicted as an electrical socket) with a 'current' passing between them; the plug was labelled 'Xalatan' with 'latanoprost' printed beneath. 'Xalatan prescribing information can be found on the back cover' was printed at the bottom of the front cover. The depiction of the electrical plug and socket was repeated on the inside pages of the SPC.

Allergan alleged that the Xalacom SPC was in effect a promotional piece as the promotional visual appeared on the front cover; small versions of it were used in place of numbers to indicate the start of different sections; it stated 'new' on the front and Xalatan prescribing information was included on the back cover. Allergan alleged that the SPC was disguised promotion.

The Panel noted that the Code stated that the term 'promotion' did not include SPCs as provided for in European Directive 65/65. (Although Council Directive 65/65 was no longer in force identical requirements were in Article 11 of the codified Council Directive 2001/83/EC.) Although SPCs *per se* were not, therefore, considered to be promotional items, the Panel considered that there could be circumstances where their use, appearance or content could, nonetheless, mean that the Code became relevant. There could be circumstances where, even as a non-promotional item, an SPC was used for a promotional purpose, or there could come a point where embellishment and/or augmentation of an SPC meant that it became a promotional item in its own right.

The Panel considered that use of the Xalatan product name on the product visual, which had triggered the requirement to provide prescribing information, meant that the Xalacom SPC promoted Xalatan.

The document itself was colourful and glossy. In the Panel's view this was not necessarily a problem. The Panel was concerned that the heading to the document was 'New Xalacom'. The Panel considered that 'new' was a claim for the product which went beyond the information found in an SPC.

The Panel considered that the augmentation of the SPC was such that the document had become a piece of promotional material for both Xalacom and Xalatan. It was therefore subject to the Code. The document purported only to be an SPC for Xalacom and that was not so. The Panel considered that the promotional nature of the document had been disguised and a breach of the Code was ruled.

Allergan Limited complained about a Xalacom summary of product characteristics (SPC) (ref P6605/8/01 391-0007) issued by Pharmacia Limited. Xalacom was an eye drop solution containing latanoprost and timolol. Pharmacia also marketed eye drops containing only latanoprost (Xalatan).

The SPC was a 12 page, A5 document printed on glossy card. The dark blue front cover was headed with 'New Xalacom'; the word 'new' was boxed and the letter X of Xalacom was in a logo form. Below the product name were the non-proprietary names and below these in turn was 'Summary of Product Characteristics'. This information appeared in a band of white towards the top of the page. The front cover also featured a representation of the components of Xalacom ie Xalatan, latanoprost (depicted as an electrical plug), and timolol (depicted as an electrical socket) with a 'current' passing between them; the plug was labelled 'Xalatan' with 'latanoprost' printed beneath. 'Xalatan prescribing information can be found on the back cover' was printed at the bottom of the front cover.

The inside pages of the SPC were printed alternately white on blue and blue on white. The headings to various sections were printed in turquoise. Beside each heading name, where there would normally be a number denoting the section, and in the bottom right hand corner of each right hand page, the depiction of the electrical plug and socket was repeated.

COMPLAINT

Allergan noted that although Clause 1.2 of the Code stated that promotion did not include summaries of product characteristics as provided for in European Directive 65/65, the company considered that the Xalacom SPC was in effect a promotional piece, contrary to this Directive, as: the promotional visual appeared on the front cover; small versions of the visual were used in place of numbers to indicate the start of different sections; 'new' was stated on the front; and Xalatan prescribing information was included on the back cover. Allergan alleged that the SPC was disguised promotion, in breach of Clause 10.1 of the Code.

RESPONSE

Pharmacia noted, as acknowledged by Allergan, that SPCs were excluded from the remit of the Code, as set out in Clause 1.2.

The information required by the European Directive 65/65 with regard to the contents of an SPC had been fully provided. The Directive did not preclude the use of product visuals, use of the word 'new' or inclusion of product prescribing information. All subsections had been numbered in accordance with the layout as recommended in the Directive.

The text of the Xalacom SPC had been approved by the Medicines Control Agency (MCA); a copy of the approval letter from the MCA was provided.

In summary, Pharmacia considered that the Xalacom SPC complied with all regulatory requirements, and it refuted the claim that it constituted disguised promotion, as no promotional claims were included within the material.

PANEL RULING

The Panel noted that whether the Xalacom SPC satisfied the legal requirements for SPCs was a matter for the MCA and not for the Authority. The Panel's remit was to decide whether the SPC was subject to the Code and if so whether it was in breach of it or not.

Clause 1.2 of the Code stated that the term 'promotion' did not include SPCs as provided for in European Directive 65/65. (The Panel noted that Council Directive 65/65 was no longer in force; the present requirements were to be found in Article 11 of the codified Council Directive 2001/83/EC. The requirements were however identical.) Although SPCs *per se* were not, therefore, considered to be promotional items, the Panel considered that there could be circumstances where their use, appearance or content could, nonetheless, mean that the Code became relevant. There could be circumstances where, even as a non-promotional item, an SPC was used for a promotional purpose, or there could come a point where embellishment and/or augmentation of an SPC meant that it became a promotional item in its own right.

The front cover of the Xalacom SPC featured a product visual (the electrical plug and socket) which carried the Xalatan product name together with its non-proprietary name latanoprost. The Xalatan prescribing information was printed on the back cover. The Panel considered that use of the Xalatan product name on the product visual, which had triggered the requirement to provide prescribing information, meant that the Xalacom SPC promoted Xalatan.

The document itself was colourful and glossy. In the Panel's view this was not necessarily a problem. The Panel was concerned that the heading to the document was 'New Xalacom'. The Panel considered that 'new' was a claim for the product which went beyond the information found in an SPC. In that regard the Panel noted that a document issued by the European Commission, 'A guideline on summary of product characteristics', which gave advice on the composition of SPCs, stated that their content could not be changed except with the approval of the originating competent authority. The Panel considered it unlikely therefore that the text of an SPC would ever describe a product as new as this was a subjective description dependent on time. The front cover featured a product visual which referred to another product brand name, Xalatan, and this was repeated throughout the document. The Panel noted Pharmacia's submission that the European Directive did not preclude the use of product visuals, the word new or the inclusion of prescribing information. The European Commission document was silent upon these issues.

The Panel considered that the augmentation of the SPC in question was such that the document had become a piece of promotional material for both Xalacom and Xalatan. It was therefore subject to the Code. The document purported only to be an SPC for Xalacom and that was not so. The Panel considered that the promotional nature of the document had been disguised; a breach of Clause 10.1 was ruled.

Complaint received **21 January 2002**

Case completed **27 February 2002**

CODE OF PRACTICE REVIEW – MAY 2002

Cases in which a breach of the Code was ruled are indexed in **bold type**.

1155/3/01	3M Health Care v Norton Healthcare	Cactus prescribing service	No breach	No appeal	Page 3
1191/6/01	**Anonymous v Organon Laboratories**	**Meetings and hospitality**	**Breach Clause 9.1 Two breaches Clause 19.1**	**No appeal Report from Appeal Board to ABPI Board**	**Page 8**
1222/8/01	**GlaxoSmithKline v Pfizer**	**Relpax Clinical Summary**	**Breaches Clauses 4.1, 7.2 and 7.8**	**Appeal by complainant**	**Page 12**
1247/11/01 & 1248/11/01	**Shire v Pfizer and Pharmacia**	**Summary of COX-2 review**	**Breaches Clauses 3.2 and 4.1 Four breaches Clause 7.2**	**No appeal**	**Page 29**
1249/11/01	**GlaxoSmithKline v Aventis Pasteur MSD**	**Promotion of Viatim**	**Three breaches Clause 7.2 Two breaches Clause 7.4 Breach Clause 15.9**	**Appeal by respondent**	**Page 36**
1253/11/01	**Pharmacia/Director v GlaxoSmithKline and GlaxoSmithKline Consumer Healthcare**	**Promotion of Zyban and NiQuitin CQ**	**Three breaches Clause 7.2 Two breaches Clause 7.3 Breach Clause 7.4**	**No appeal**	**Page 44**
1254/11/01	Primary Care Group Prescribing Adviser v Novartis	Starlix Study	No breach	No appeal	Page 50
1257/11/01	**Pfizer v Bayer**	**Promotion of Adalat LA**	**Five breaches Clause 7.2 Two breaches Clause 8.1**	**No appeal**	**Page 53**
1258/11/01	Aventis Pasteur MSD v GlaxoSmithKline	UK Guidance on Best Practice in Vaccine Administration	No breach	No appeal	Page 60
1260/12/01	**AstraZeneca v Wyeth**	**Promotion of Prostap**	**Three breaches Clause 7.2 Breaches Clauses 7.4, 7.8 and 8.1**	**No appeal**	**Page 66**
1261/12/01	**Schering-Plough v UCB Pharma**	**Promotion of Xyzal**	**Breach Clause 4.6 Eleven breaches Clause 7.2 Three breaches Clause 7.3 Two breaches Clause 7.4 Breach Clause 7.9 Two breaches Clause 7.10 Breach Clause 8.1**	**No appeal**	**Page 70**
1265/12/01	**General Practitioner v Novartis**	**Failure to correctly position the non-proprietary name**	**Breach Clause 4.3**	**No appeal**	**Page 83**

1267/12/01	Paragraph 17 v Ivax (Norton)	Cactus prescribing service	No breach	No appeal	Page 84
1268/12/01	**Bristol-Myers Squibb and Sanofi-Synthelabo v Novartis**	**Diovan detail aid**	**Breach Clause 3.2**	**No appeal**	**Page 87**
1269/1/02	**Forest Laboratories v Chiron Corporation**	**Promotion of Tobi**	**Eight breaches Clause 7.2 Breach Clause 7.3 Six breaches Clause 7.4 Breaches Clauses 7.8 and 7.10**	**No appeal**	**Page 89**
1271/1/02	**Allergan v Pharmacia**	**Xalacom summary of product characteristics**	**Breach Clause 10.1**	**No appeal**	**Page 96**

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, administer, recommend 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
- the provision of information to the general public either directly or indirectly, including by means of the Internet
- 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).