PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 23

FEBRUARY 1999

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.

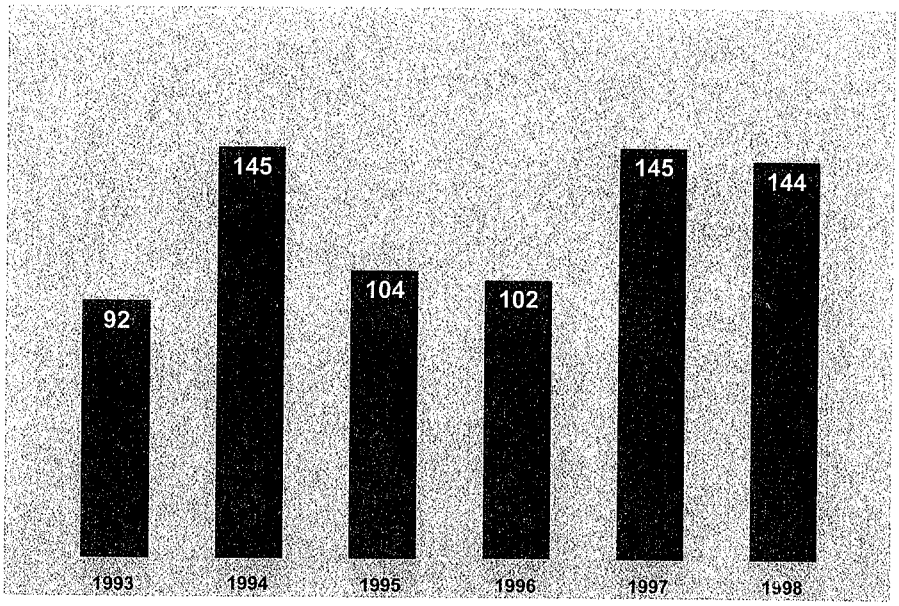
Level of complaints remains high

There were 144 complaints under the Code in 1998 as compared with 145 in 1997. There were 104 in 1995 and 102 in 1996.

The number of cases differs from the number of complaints because some complaints involve more than one company and because some complaints do not become cases at all, usually because no prima facie breach is established. There were 139 cases in 1998 as compared with 165 in 1997.

The largest number of complaints in 1998 came from health professionals, 44% coming from health professionals and 34% from other pharmaceutical companies.

There have been wide but unexplained variations in the number of complaints received each year since the Authority was established at the beginning of 1993, ranging from 92 in 1993 to 145 in both 1994 and 1997.



Dr Brian Lewis

The Authority received with sadness the news that Dr Brian Lewis had died on 8 January. Brian was one of the first two independent medical members of the Code of Practice Committee who were appointed in 1978. Since then he had served continuously in that capacity, first on the Committee and later on the Code of Practice Appeal Board.

Never reluctant to speak his mind, sometimes to the discomfiture of company representatives appearing in relation to appeals, he made a valuable contribution to the work of the Committee and the Appeal Board and was a staunch supporter of self-regulation by the industry of its promotional activities. He will be much missed.

Doctors seeking payment from representatives

Companies are reminded that Clause 15.3 of the Code of Practice states that "Representatives must not employ any inducement or subterfuge to gain an interview. No fee should be paid or offered for the grant of an interview".

It is occasionally reported that doctors are seeking payment of some sort and the Authority draws to the doctors' attention the requirements of the Code and UK law in this regard.

In a recent instance representatives were invited to either make a "voluntary" contribution of £20 per doctor to an equipment fund or provide an item of equipment likely to be of benefit to patients.

Compliance with such requests would be in breach of the Code whether "voluntary" or not and companies are asked to ensure that their representatives are aware of the position. It is from time to time claimed by doctors that representatives have gone along with such requests.

Inter-company settlement of disputes

While the Authority will consider any complaint which is made to it, and inter-company complaints make a valuable contribution to self-regulation, companies are reminded that it is the view of The Association of the British Pharmaceutical Industry (ABPI) that they should try to settle inter-company disputes between themselves before submitting complaints to the Authority. This view was restated at a recent meeting of the ABPI Board of Management.

Please circulate the Review

Those receiving the Code of Practice Review at pharmaceutical companies and agencies etc, are reminded that it should be circulated to all those responsible for the preparation or approval of promotional activities. It is the sole source of information about current developments and rulings and can assist companies in their wish to stay within the requirements of the Code of Practice.

Stop Press... ... new regulations

The Medicines (Advertising and Monitoring of Advertising) Amendment Regulations 1999 (SI 1999 No 267) were made on 5 February and come into operation on 5 April. Copies can be obtained from branches of HMSO.

The changes were the subject of consultative document MLX 239 issued by the Medicines Control Agency (MCA) on 21 August 1997.

It is anticipated that the MCA will publish guidelines on the advertising and promotion of medicines to coincide with the coming into force of the new regulations.

The regulations are intended to

- clarify the meaning of "persons qualified to prescribe or supply"
- set out the powers available to the MCA to regulate the advertising and promotion of medicines
- clarify the relevance of the regulations to centrally authorized products
- require all advertisements to comply with the summary of product characteristics, encourage rational use and not be misleading
- prohibit the provision of samples to the public for promotional purposes

CODE OF PRACTICE TRAINING

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

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

Forthcoming Code of Practice seminar dates are:

Friday, 28 May

Friday, 25 June

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 Jane Landles.

How to contact the Authority

Our address is:

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

Telephone: 0171-930 9677
Facsimile: 0171-930 4554

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Jane Landles.

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

Heather Simmonds: 0171-747 1438
Etta Logan: 0171-747 1405
Jane Landles: 0171-747 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.

CASE AUTH/700/4/98

GENERAL PRACTITIONER v ASTRA

Losec bonus scheme

A dispensing general practitioner complained about the provision of Losec bonus stock by Astra. It was alleged that the practice had an agreement with Astra to receive a bonus of one free pack of Losec (omeprazole) 20mg for every ten packs purchased but had not received the bonus since 1996 despite having purchased 440 packs. The practice had contacted Astra's representatives and its head office but without satisfaction. Astra's response to the complaint was sent to the complainant who submitted further comments. The two parties gave detailed but differing accounts of the series of events involved.

The Panel noted that the dispute between the parties had existed for some time and was concerned that Astra had failed to resolve matters at an earlier stage. Communications between the parties had broken down. There was a fundamental disagreement as to the nature and extent of the business arrangement which existed with regard to bonus stock of Losec. However, given the parties' differing accounts and interpretations of events it was not possible to determine precisely what had happened and the Panel accordingly ruled no breach of the Code.

Upon appeal by the complainant, the Appeal Board noted that Astra stated that it did not operate a bonus scheme of discounting wholesaler stock by the provision of one pack of 28 Losec 20mg free for every 10 packs purchased and that this policy had been in place for at least the last three years. According to Astra it had provided 5 packs of 28 Losec 20mg to the practice in 1996 as a gesture of goodwill on a retrospective basis. The Appeal Board considered that Astra had changed its policy on the provision of retrospective bonus stock but had failed to clearly advise the complainant who had been left with the impression that the company was under a continuing obligation to provide retrospective bonus stock. The complainant had stated that he and his staff had raised their concerns with Astra representatives and head office. The Appeal Board considered that Astra had mismanaged the situation and should have made greater efforts to clarify the situation regarding retrospective bonus stock.

The Appeal Board considered that overall the company had failed to maintain a high standard and ruled a breach of the Code in that regard.

A dispensing general practitioner submitted a complaint about the provision of Losec (omeprazole) bonus stock by Astra Pharmaceuticals Ltd.

COMPLAINT

The complainant stated that since September 1996 the practice had received no agreed bonus of one pack of 28 Losec 20mg free for every 10 packs purchased. From this date, the practice had purchased 440 packs totalling well over £13,000 but as yet no bonus stock had been received, or appeared to be forthcoming, from Astra.

Between September 1996 and May 1997 no sales representative called in at the surgery to collect the copy invoices in order to allocate bonus stock relating to the sales. This time lapse of 9 months was inexcusable and unprofessional. However, when an Astra representative appeared at the surgery in May 1997 and was informed of the situation, the practice dispenser was assured "that the problem would be sorted out and that he would not let the surgery down". Between May and August the representative appeared regularly to collect the copy invoices but still no bonus stock had been received. This led to the practice dispenser contacting Astra head office in a bid to speak to two particular people for their help in the matter but to no avail. They were never available and never returned any calls. Deeply concerned the practice dispenser sent a facsimile to both of these members of Astra's staff. In April 1998 the facsimiles had not yet been answered.

The complainant stated that in between times, the representative had appeared only twice, once assuring the practice dispenser that the matter was "in hand" and the second time, after being offensive, informing her that he had "given up on it".

The complainant provided the Panel with copies of invoices, chosen at random, to show how the system was supposed to work, copies of the facsimile messages sent to Astra head office and a card from an Astra area sales manager, which was issued in 1995, by way of a receipt for invoices collected at that time.

RESPONSE

Astra stated that it did not operate a bonus scheme of discounting wholesaler stock by provision of one pack of 28 Losec 20mg free for every 10 packs purchased and could confirm that this policy had been in place for at least the last three years.

About three years ago, the practice approached the area sales manager to claim retrospective Losec bonus stock which it stated was due to it. This accounted for the hand-written receipt from the area sales manager dated 16 March 1995 which was enclosed with the letter of complaint. The arrangements under which the bonus stock was claimed were unclear, but as a gesture of goodwill five packs of 28 Losec 20mg were provided to the practice on 20 February 1996 by Astra head office on a retrospective basis.

The practice did not have a direct account with Astra. The invoices enclosed with the letter of complaint showed that the practice bought Losec 20mg from a wholesaler and not direct from Astra. Astra had tried to establish a contract with the practice over two years ago but it understood that this was refused on the grounds that the practice did not enter into contracts with companies. On this basis, there was no reason for the practice to expect bonus stock from Astra. Astra stated that if the practice had evidence of any current bonus arrangement with Astra it would wish to know about it as this would require a disciplinary review of the staff involved.

Astra had discussed the complaint with the representative concerned who confirmed that there was no contract arrangement between Astra and the practice.

Astra was puzzled by the account of various contacts with Astra described by the complainant. It was stated that between September 1996 and May 1997 no sales representative called at the surgery to collect copy invoices; this was because there was no contract between the practice and Astra. Astra stated that on this basis it did not accept that the time lapse of 9 months was inexcusable and unprofessional, as alleged.

Astra confirmed that its representative collected copy invoices from the practice on one occasion in early 1997 in an attempt to investigate the matter further.

It was also stated in the letter of complaint that the practice dispenser contacted Astra head office after August 1997 to speak to two members of staff. At the time one was no longer employed by Astra and the other had been working in another area of the company for some time. It was not clear who the practice dispenser had spoken to but had she spoken to Astra customer services, she would have been so informed.

With regard to a copy of a facsimile from the dispenser dated 4 September 1997, Astra noted that there was no confirmation slip that the facsimile had been transmitted and Astra had no record of having received the facsimile. The facsimile number cited was a confidential number with limited distribution and it was highly unlikely that receipt of a facsimile on that number would have been overlooked.

It was stated by the complainant that the representative made two calls at the practice during what appeared to be late 1997/early 1998. He had confirmed that despite meeting with the practice on a regular basis during 1997/1998 no mention was made about the practice's concern regarding the alleged outstanding retrospective bonus and that no further wholesaler invoices were presented to him.

Astra confirmed that the representative had been employed by Astra for more than 2 years. He had 25 years' experience of working in the pharmaceutical industry, had passed the ABPI representatives examination and operated to high standards as expected by Astra. Astra had not found any evidence that his behaviour had led to any breach of Clauses 15.2 and 9.1 of the Code.

Astra submitted that in summary, it did not believe that there was a case to answer as the practice did not have a contract with Astra and there were no arrangements for provision of Losec bonus stock. On this basis, there were no grounds for a breach of Clause 18.1 and it denied any alleged breach of Clause 18.1. Furthermore, it did not accept any breach of Clauses 15.2 and 9.1 with regard to the conduct of its representative.

* * *

Prior to making a ruling the Panel decided to send Astra's response to the complainant for comment.

FURTHER COMMENTS FROM THE COMPLAINANT

The practice dispenser replied on behalf of the general practitioner. The practice dispenser had recently acquired a flow chart which showed various options open to Astra representatives in terms of awarding bonus stock. A copy was provided to the Panel on which the dispenser had highlighted the practice requirements. This chart, only recently obtained, was believed to be currently active, and was in line with the agreement made with an Astra representative in 1994. At no time had there been notice of any change to the original agreement, therefore the surgery expected the bonus as shown in the chart and originally agreed to be ongoing.

The surgery approached Astra's area sales manager over three years ago to question the whereabouts of the bonus stock which was due since the time the agreement had been made. Seven invoices were presented to him and a receipt was obtained. He was then to arrange retrospective bonus relating to the seven invoices and several previous copy invoices. A month earlier the area sales manager and a colleague had attended the surgery to ask for a contract to be signed. The surgery declined, as it would limit the doctors' freedom to prescribe and supply whichever product best suited each individual patient's needs. This was due to the contract insisting on the surgery purchasing a pre-set number of Losec packs per annum. The surgery could not guarantee to reach or maintain the pre-set figure. The gentlemen concerned were disappointed with the decision but there was no mention of the previously agreed bonus being withdrawn.

At the meeting in March 1995 the area sales manager accepted the invoices and did not advise of any change to the bonus system. After hearing nothing more from the area sales manager, or indeed from Astra, for some time, the dispenser contacted two members of Astra's head office staff and asked their help to resolve the matter. The dispenser found them to be very helpful and from the initial contact with these employees through until 13 February 1996, the surgery received six separate deliveries of Losec 20mg as bonus for the stock purchased between 1994 and February 1996. This bonus stock amounted to 56 packs. Delivery notes were available showing these had been received. The dispenser was not advised of any "gesture of goodwill". At no time was it suggested by Astra that this delivery of bonus stock was anything other than that.

The surgery did not have a direct account with Astra but it had "data release mandates" with other companies for the provision of retrospective bonus stock. This option was recently suggested to Astra's representative as an alternative to a contract but no comment was made by him. Although no contract or agreement had been signed by either party, at any time, it had to be said that if any representative initiated a bonus, or discounting scheme, the customers expected it to have the full backing and authority of the company and therefore be honoured by the company. The only evidence the practice could present was the standard flow chart and the fact that the precedent was set when the practice received the 56 packs between 1994 and 1996 for stock used during this period.

Between September 1996 and May 1997 no sales representative called at the surgery, whether to collect copy invoices or even as a courtesy call. The surgery, throughout this time, still did not receive any notice of a

change in bonus policy and therefore a bonus entitlement was still expected.

In May 1997 Astra's representative was happy to accept copy invoices for the purpose of issuing bonus stock and indicated it should arrive in approximately two weeks. He did not indicate that the bonus scheme was outdated or that any investigation was necessary.

In August 1997 the bonus stock promised by the representative had still not arrived despite being questioned on at least one occasion since his first meeting with the practice in May. This prompted the dispenser to contact the two people at Astra's head office, bearing in mind the help she had received before. She was not informed that one of them had left the company, or that the other had re-located, nor was she advised of their replacements. Having had no telephone success, a letter was sent by facsimile stating the problems the practice was having. This was sent to two separate facsimile numbers, within Astra, using the direct lines. It might be "highly unlikely" for these facsimiles to have been overlooked on these numbers but it would appear to have been possible.

The subject discussed during the representative's meetings with the practice in late 1997 and early 1998 was the whereabouts of the retrospective bonus stock from 1996 onwards. These discussions included other members of the practice staff as well as the dispenser who found it insulting to read that no mention was made about outstanding retrospective bonus. The representative had even stated on one occasion "Oh! I've given up on that".

Since contacting the Authority the surgery had received several visits from the representative, and also a phone call on behalf of the regional area sales manager requesting information so that a contract could be drawn up. The caller seemed surprised when she was informed of the situation at present.

PANEL RULING

The Panel observed that the complainant and respondent had provided differing accounts of the events in question. It was difficult in such cases to know exactly what had transpired between the parties. The Panel accepted, however, that extreme dissatisfaction must be necessary on the part of an individual before he or she submitted a complaint. A judgement had to be made on the available evidence.

The Panel noted that the practice had provided a photocopy of a hand-written receipt from an Astra area sales manager which read "Received, copy invoices Jan/Feb relating 70 x 28 Losec 20mg = 10% bonus due". The receipt was signed and dated 16 March 1995. The Panel noted Astra's submission that although unaware of the basis for such a bonus, five packs of 28 Losec 20mg were provided as a goodwill gesture in February 1996. The Panel noted the complainant's submission, however, that between March 1995 and February 1996 56 packs of Losec had been received as a bonus for the stock purchased between 1994 and February 1996.

The Panel noted that the complainant referred to an agreement regarding bonus stocks of Losec made with an Astra representative in 1994. This agreement was stated to be in line with the flow chart provided. The Panel did not know the status of the flow chart; although clearly related to Losec it was not dated.

The Panel noted that the dispute between the parties had existed for some time and was concerned that Astra had failed to resolve matters at an earlier stage. Communications between the parties had broken down. There was a fundamental disagreement as to the nature and extent of the business arrangement which existed with regard to bonus stocks of Losec. However, given the parties' differing accounts and interpretations of events it was not possible to determine precisely what had happened and the Panel accordingly ruled no breach of Clauses 18.1, 15.2 and 9.1 of the Code.

APPEAL BY THE COMPLAINANT

The complainant stated that in 1994 the representative for Astra initiated a bonus scheme whereby the practice purchased Losec 20mg from a nominated wholesaler and provided Astra with copies of the invoices for the company to provide bonus stock retrospectively. This the practice did and had continued to do so. The practice had no doubt that this scheme was approved by Astra and at no time then, or since, had Astra informed it of any change. The complainant asked whether this constituted a breach of Clause 15.10. While the practice was awaiting the Panel's ruling it was informed that this system was "illegal" and the practice "didn't have a hope of winning [its] case." That said, the complainant was led to believe this system was actually endorsed by the ABPI which was probably why so many other major pharmaceutical companies used it with dispensing practices. The complainant had also spoken with a former Astra representative, who confirmed that Astra operated a retrospective bonus scheme of 1 pot free of charge for 10 pots purchased from the company in 1996; she remembered collecting invoices to give to the area sales manager. They both then signed a form for the regional manager to send to Astra head office. where the dispatch of retrospective bonus to the practice was authorised.

The complainant stated that the flow chart supplied to the Panel was shown to the practice as recently as June 1998 and showed clearly how the bonus scheme was supposed to operate. The complainant believed it originally came from the regional manager. Astra might well deny its existence but it clearly stated Losec as a product. It also named a specific employee. Could Astra confirm her position within the company, whether or not she was currently employed and/or the date she left the company? The procedure should normally take two weeks which the former Astra representative was willing to confirm.

The complainant said that the former representative could verify the system's existence. How could Astra deny its validity when senior personnel still referred to it?

The complainant said that the practice's use of Losec 20mg for the total period 1994 to February, 1996 was 560 pots of Losec. As the practice claimed, bonus was due at 1 pot in 10 and would equate to the bonus stock totalling 56 pots of 28 Losec. Copies of delivery notes from Astra showed that the practice had received, not five pots of Losec, as the company claimed, but 56 pots of Losec, delivered in six shipments over an 11 month period. The

practice had always believed this to the be the bonus stock due to it. At no time was a "goodwill gesture" mentioned. Furthermore, this alleged "goodwill gesture" by Astra took nearly one year to be sent, a long time if it was trying to placate customers upset by a lack of service. As the stock was clearly labelled Losec, the complainant questioned a breach of Clause 18.1. The system was confirmed by Astra's provision of this bonus stock due under the terms set out by its representative back in 1994 and which the practice had no reason to believe had changed. The complainant stated that the wholesaler concerned was willing to confirm the practice's use of Losec if required. The wholesaler also indicated that the practice was not alone in the problems it was experiencing but would require signed mandates before releasing any information.

The complainant stated that the contact with Astra head office dated back to 1995 when the practice dispenser had discussions with two members of staff regarding the provision of bonus stock. The two employees held senior positions within the company and the practice's attempts to contact them again for help regarding the similar matter in 1997 were because nobody else employed by Astra seemed willing or able to sort out the problem. The practice had their direct facsimile numbers from its previous contact and would presume that anyone collecting messages at that level would make sure that the appropriate persons, or replacements, received them. The complainant stated that for Astra to suggest the facsimiles were somehow overlooked would appear convenient and negligent.

The complainant noted that, according to Astra, its representative claimed that in early 1997 he collected invoices to "investigate the matter" yet when he took the invoices, he told the practice dispenser, in front of other staff, "You will get your bonus in about two weeks". It was also stated, in Astra's response, that no mention was made to the representative about the practice's concern regarding outstanding bonus. This was completely false as all members of staff asked him about the outstanding bonus stock on every occasion he visited the surgery. On the last occasion, he even replied "I've given up on it". The staff were upset by these allegations and the complainant enclosed letters confirming their witness to his being asked. The complainant considered that this might constitute a breach of Clause 15.2. Since the practice's initial contact with the Authority, the representative had told the practice, "The head ones are jumping to get this sorted out. It's embarrassing when the managing director is on the ABPI Board". If this was the case, why had the area sales manager, or someone senior to him, not had a meeting to try to resolve the matter. The practice had been harassed with claim and counterclaim, eg "did not stand a chance of winning", "haven't got a leg to stand on" and the practice was even asked to "Drop the case". When the practice pointed out that it had nothing to lose in pursuing the matter, a suggestion was made that if the practice signed a (backdated) contract to 1997, Astra would provide some bonus stock and "that would be better than none". The inference was that if the practice didn't sign, Astra would give the practice nothing. The practice declined, questioning the legality of such a move. The practice also questioned a breach of Clause 18.1. The practice had also had telephone calls from Astra's contracts department to draw up a contract without the practice having requested one. Whether it was to be for 1997, or 1998, the practice was unaware.

In short, the practice considered that it had been treated very badly by a large pharmaceutical company which had reneged on a verbal agreement between the practice and the representative. The company had refused to accept the evidence confirming the practice's position and it and some of its employees had acted in an unprofessional and discourteous manner. The practice considered that the Code covered some of these points and hoped that its appeal would be viewed in a complete and unbiased way, with consideration of its initial response and these more detailed additions. Only those conversations with staff which had been witnessed had been retold. There had been others but they could not be corroborated.

RESPONSE FROM ASTRA

Astra made the following comments about the alleged breaches of the Code:

Clause 18.1 The practice was a dispensing practice and the recent discussions regarding Losec had taken place in this context. During the period under complaint there was no evidence that any gift, benefit in kind or pecuniary advantage had been offered or given as an inducement to prescribe, supply, administer or buy Losec. Efforts had been made to establish an Astra dispensing contract with the practice. The complaint centred on the absence of bonus stock and not the presence of an inducement.

Clause 15.2 Astra considered that the representative concerned had maintained a high standard of ethical conduct in compliance with the Code and had made considerable efforts to try to resolve a difficult situation.

Clause 9.1 Astra considered that high standards had been maintained. The company had already commented on the various contacts between the practice and Astra.

Clause 15.10 As stated previously, Astra did not operate a bonus scheme of discounting wholesaler stock of Losec and confirmed that this policy had been in place for at least the last three years. This was consistent with the dates of delivery notes provided by the complainant: five were dated 1995; the final delivery of 5 packs in February 1996 was made as a gesture of good will on a retrospective basis. Astra had commented on the flowchart provided by the practice. On this basis the representative did not, and was not able to, provide Losec bonus stock. Astra therefore maintained that there had not been a breach of Clause 15.10.

Astra stated that it was very concerned that the complainant was dissatisfied with the practice's relationship with the company and Astra had tried to resolve this matter by contact with the practice and with the offer to establish an Astra dispensing contract. Astra set high standards for the behaviour of its staff and it would expect that any contact with the practice would have been dealt with in a professional and courteous manner. There were clearly differing accounts of events which made it difficult to establish what had happened.

Astra would like to re-establish a good working relationship with the practice and was willing to send a senior member of the management team to meet with the complainant.

In summary, Astra maintained that there had been no breach of Clauses 18.1, 15.2 and 9.1 of the Code, in accordance with the Panel's ruling. In addition, Astra did not accept that there had been a breach of Clause 15.10 as raised in the complainant's letter of appeal.

In addition Astra supplied a letter of response from its relevant Field Sales Manager which covered the following points:

Purported use of a retrospective Losec bonus scheme and corroboration from a former Astra representative

- Some 3-4 years ago the area sales manager, and the then key accounts manager were in receipt of invoices from the practice. Following this contact a small volume of Losec was provided. Since this event no further quantities of Losec had been provided. The area sales manager had confirmed that only those practices which signed a dispensing contract with Astra were eligible for bonus stock.
- The statement that a former Astra representative could confirm the existence of a retrospective bonus scheme as late as 1996 must be treated with caution. The area sales manager had confirmed that there were disciplinary issues with this employee prior to her resigning from Astra. At no point did the area sales manager receive invoices from the representative while she was employed with Astra.

Flow chart

- The document would appear to have been produced some time ago as an internal training document by Astra representatives in another region. The individual named on the flow chart was an experienced medical representative from that sales team.
- It would appear that the flow chart might have been shown inadvertently to the practice by the Astra representative.
- The flow chart provided by the practice had not been sanctioned by any senior Astra manager. The practice dispenser was incorrect in her assertion that the flow chart came originally from a senior manager.

Alleged conversations between the representative and the practice

- It was difficult to comment on statements attributed to the representative, as the context of the alleged conversations was not available.
- On taking over responsibility for this practice in May 1996, the representative had concentrated on promoting Losec. He had confirmed that on one occasion he was given invoices by the dispenser in order to investigate the matter. He cannot recall saying that they would get their bonus stock in two weeks as this event took place some 18 months ago.
- The representative had been in contact with the practice on a regular basis in the past year and had stated that he was not asked about bonus stock continually.
- The representative, the area sales manager and the then field sales manager tried recently to arrange for the practice to sign an Astra dispensing contract, as this was the only way any dispensing practice could receive bonus stock for Losec. This avenue was pursued in June 1998 as a means of establishing a better relationship with the practice. The practice turned this down, which the representative had stated related to his comments that "I've given up on it".

Additional background information

- It was important to note that no other practice in the same region had commercial issues with Astra.

FURTHER COMMENTS FROM THE COMPLAINANT

In relation to Astra's comments regarding specific clauses of the Code, the complainant noted the following:

Clause 18.1 While the practice's main concern was the absence of bonus stock due under terms agreed in 1994 and never contravened, the practice considered it almost certainly covered the offer of bonus stock only if it signed a backdated contract to 1997 tying the practice to prescribe and supply a pre-determined amount of Losec per month for a one year period. If the practice did not agree to use this amount it did not receive any bonus. The practice considered this was an inducement to prescribe, supply and purchase medicine and constituted a breach of the Code.

Clause 15.2 "There were clearly differing accounts of events" the complainant agreed entirely with this and asked the Appeal Board to favour the account provided by the practice given that it was substantiated by witnesses to the conversations as already stated. It was the complainant's view that a high standard of ethical conduct had not been adhered to hence a breach of the Code.

Clause 9.1 The lack of communication and other complaints as detailed, in the complainant's view, did not equate to a high standard.

Clause 15.10 Astra claimed that it did not bonus on wholesaler purchase stock and had not done so for three years. This would indicate that it did operate a bonus scheme on wholesaler purchased stock prior to 1995. The bonus agreement between the practice and Astra started in 1994 and had never been contravened. Therefore the practice expected it to be honoured.

Astra did not deny that it provided bonus stock using the method the practice had indicated and as detailed on the flow chart. The area sales manager received invoices from the practice dispenser and from the former representative, as previously stated, and must have authorised bonus stock up to 1996, ie 2 years ago. Since this agreement had not been contravened the practice maintained that the area sales manager, and/or the representative should have authorised the provision of bonus stock or should have liaised with the practice on this matter. The practice therefore questioned a breach of Clause 15.10.

The complainant noted that Astra claimed to be very concerned with the practice's dissatisfaction with the company and its representatives. If so why did the company not concede a breakdown in communication had occurred and since the practice was unwilling to

accept what it considered was a clear inducement to prescribe and supply Losec by signing a contract, the practice suggested that a possible solution would be for Astra to accept the practice's proven use of Losec for the period 1 March 1996 to 30 September 1998 and honour the terms as originally agreed, ie one pot free of charge for 10 pots purchased. From 1 October 1998 the practice would sign a mandate for the wholesaler to provide Astra with details of stock purchased in order to facilitate bonus stock. This was suggested to the representative, by the practice dispenser, earlier this year, but nothing came of it. The practice considered that this complied with the Authority's rules and regulations and had been adopted by some dispensing doctor surgeries and Astra. This way the practice would receive what it considered it was due and perhaps the practice and Astra could then go forward and a better working relationship might be possible.

The complainant then turned to the comments made by the field sales manager.

Purported use of a retrospective Losec bonus scheme and corroboration from a former Astra representative

The complainant stated that the date was ambiguous - the complainant could confirm the actual date of the visit was 28 February 1995, the area sales manager was given copy invoices. The practice received 56 pots of Losec from Astra and if this was "a small volume" - so be it - the actual amount given had not been stated by Astra. Since February 1996 no bonus stock had been received nor had any change in circumstances been notified to the practice. In other words the bonus scheme was halted without any notice after running for two years. The statement from the former representative might well be treated with caution at the discretion of the Appeal Board, but must still be considered due to the fact that the representative was named on one of the delivery notes relating to the bonus stock in 1995. This contradicted the area sales manager's claim that at "no point did he receive invoices from the former representative", the bonus stock must have been approved by the area sales manager prior to dispatch. The area sales manager also told the practice dispenser in January of 1995 that he had "signed off the bonus the previous Tuesday". This indicated his awareness of the bonus scheme.

Flow chart

The complainant questioned how a flow chart could "inadvertently" be shown to the practice. The chart indicated a bonus scheme which Astra claimed was out of date by three years, which meant it was out of date before the current representative started with Astra, so why did he have a copy at all?

Alleged conversations between the representative and the practice

The complainant stated that most of the conversations had taken place in reception, or the dispensary, in the presence of several members of staff. The signed affidavits sent with the letter of appeal acted as proof from the practice staff concerned that they witnessed the conversations which had been previously detailed. Since the representative started calling at the practice various members of staff had told him about past difficulties in the hope they would not continue. The representative collected invoices and made no mention of any investigation. He indicated that the bonus stock would be with the practice in about two weeks and made no effort to change the scheme the practice was using to achieve bonus. At no time since had the representative admitted that he was mistaken or misinformed nor suggested a change in the bonus scheme to the practice. The representative's claim that he was not asked about bonus stock was a complete fabrication. The complainant referred to the witnesses' statements provided. Indeed it was after such question in 1997 when the representative replied "I have given up on it" which prompted the practice to write to the Authority. The representative was claiming his statement related to a meeting in June 1998. The complainant noted that the wording would have no relevant meaning if directed at the practice following rejection of a contract in June 1998. It was made over a year ago and was stated in a letter from the practice to the Authority.

APPEAL BOARD RULING

The Appeal Board noted that Astra stated that it did not operate a bonus scheme of discounting wholesaler stock by the provision of one pack of 28 Losec 20mg free for every 10 packs purchased and this policy had been in place for at least the last three years. According to Astra it had provided 5 packs of 28 Losec 20mg to the practice on 20 February 1996 as a gesture of goodwill on a retrospective basis.

The Appeal Board considered that Astra had changed its policy on the provision of retrospective bonus stock but had failed to clearly advise the complainant who had been left with the impression that the company was under a continuing obligation to provide retrospective bonus stock.

The Appeal Board expressed concern that the flow chart, which clearly related to retrospective bonusing of Losec 20mg, had not been approved by any senior manager at Astra. The company had submitted that the document was an internal training document. In addition, given Astra's submission that retrospective bonusing of Losec had stopped three years ago, the chart must have been out of date when it was shown to the surgery. Astra had to take responsibility for the actions of its representatives, including the use of the flow chart.

The Appeal Board considered that extreme dissatisfaction was usually necessary on the part of an individual before he/she was moved to submit a complaint.

The complainant stated that he and his staff had raised their concerns with Astra representatives and head office. The Appeal Board considered that Astra had mismanaged the situation and should have made greater efforts to clarify the situation regarding retrospective bonus stock.

The Appeal Board considered that overall the company had failed to maintain a high standard and ruled a breach of Clause 9.1 of the Code. The appeal was successful in this regard.

The Appeal Board upheld the Panel's rulings of no breach of Clauses 15.2 and 18.1 of the Code.

Complaint received **27 April 1998**

Case completed **11 December 1998**

CASES AUTH/715/5/98 and AUTH/716/5/98

PARKE DAVIS v BRISTOL-MYERS SQUIBB AND SANKYO PHARMA

Promotion of Lipostat

Parke Davis complained about a Lipostat (pravastatin) journal advertisement and brochure issued by Bristol-Myers Squibb and Sankyo Pharma. The main concern was that claims were being made that pravastatin might have an effect beyond simple cholesterol lowering that was not shared by other statins. There was no evidence to support this position and it was not consistent with the summary of product characteristics.

A journal advertisement claimed that Lipostat "...goes beyond class effect..." which was referenced to two studies which examined only pravastatin and simvastatin. Parke Davis contended that evidence would be needed from all or most of the class to demonstrate that effects due to pravastatin were other than class effects. A number of effects beyond cholesterol lowering had been observed with other statins but their significance in terms of therapeutic outcome was not known. Parke Davis alleged that it was inappropriate to make claims implying that there was some special attribute of pravastatin based on such limited data. A similar allegation was made by Parke Davis in relation to a brochure distributed at an international conference in Scotland.

The Panel considered that the statement in the advertisement "Lipostat also goes beyond class effect, reducing platelet thrombus formation and not inhibiting the proliferation of smooth muscle cells - both important factors in coronary heart disease" in conjunction with the strapline "Lipostat offers more than just cholesterol reduction" conveyed the impression that the reduction of platelet thrombus formation and the lack of inhibition of the proliferation of smooth muscle cells were benefits beyond lipid modification not shared by other statins. The data relating to smooth muscle proliferation was from *in vitro* studies. Whilst the reduction of platelet formation and non-inhibition of the proliferation of smooth muscle cells had been suggested as factors in coronary heart disease their significance in terms of therapeutic outcome was not known. The Panel ruled that the advertisement overstated the totality of the data and was misleading in breach of the Code. A similar ruling was made in relation to the brochure. Upon appeal by Bristol-Myers Squibb and Sankyo, the Appeal Board endorsed the view that the totality of the data had been overstated and ruled breaches of the Code in relation to both the advertisement and the brochure.

The Panel also ruled a breach of the Code in relation to a page in the brochure headed "Pravastatin - more protection than expected" which detailed the results of the WOSCOP study. Given reservations expressed in the study, that the data be viewed with caution, the Panel considered that the page prominently detailing such data was misleading and insufficiently qualified. Upon appeal, the Appeal Board considered that the claim was an accurate reflection of the WOSCOPS data and ruled no breach of the Code.

The Appeal Board upheld the Panel's ruling that there had been a breach of the Code because the brochure was more than four pages and there was no statement as to where the prescribing information could be found. Although part of the brochure came within the partial exemption in the Code in relation to promotion of unlicensed indications/products at international conferences held in the UK, the remainder of the brochure promoted indications licensed in the UK. The brochure therefore needed to comply with all the relevant requirements of the Code.

Parke Davis & Co Limited complained about the promotion of Lipostat (pravastatin) by Bristol-Myers Squibb Pharmaceuticals Limited and Sankyo Pharma UK Ltd.

Parke Davis stated that its fundamental concern was that the companies were making claims that pravastatin might have an effect beyond simple cholesterol lowering that was not shared by other members of the statin class. There was absolutely no evidence to support this position and such promotion was not consistent with the mechanism of action described in the summary of product characteristics (SPC).

Bristol-Myers Squibb and Sankyo submitted a joint response.

1 Journal Advertisement

This advertisement had appeared in a number of medical journals in the UK and carried the strapline "Lipostat offers more than just cholesterol reduction". Subsequent text claimed that "Lipostat also goes beyond class effect, reducing platelet thrombus formation and not inhibiting the proliferation of smooth muscle cells". The two claims were referenced to Lacoste *et al* (1996) and Corsini *et al* (1992) respectively.

COMPLAINT

Parke Davis stated that the strapline "Lipostat offers more than just cholesterol reduction" was not in itself untrue since beneficial reduction in heart attack risk and alterations in other parameters had been reported with Lipostat, as indeed they had with other statins. Parke Davis alleged that the use of this strapline in conjunction with the subsequent text in the advertisement clearly breached Clause 7.2 of the Code for a number of reasons:

The text stated that Lipostat "... goes beyond class effect ..." and gave two references in support of a difference, Lacoste *et al* (1996) and Corsini *et al* (1992). These studies only examined pravastatin and simvastatin. Evidence would be required from studies of all or most of the class to truly demonstrate that the effects due to pravastatin were anything other than class effects. Furthermore, a number of effects beyond cholesterol reduction had been seen with other statins, although, as with pravastatin, their significance in terms of therapeutic outcome was not known. Parke Davis alleged that it was inappropriate and in breach of Clause 7.2 of the Code to make claims

implying that there was some special attribute of pravastatin based on such limited data.

Parke Davis stated that Corsini *et al* (1992) was not a clinical study but an *in vitro* investigation comparing the effects of pravastatin and simvastatin on rat and human myocytes. Apart from the difficulties in extrapolating results from these investigation models to patients, Parke Davis was concerned that the advertisement claimed benefits from not inhibiting the proliferation of smooth muscle cells and that pravastatin was "... no less than your patients deserve." Not only was it difficult to support patient benefit claims on the basis of this laboratory *in vitro* work, but this area of research and its clinical interpretation remained highly controversial. The balance of informed scientific opinion was that inhibition of smooth muscle cell proliferation should be expected to have a more beneficial effect on the atherogenic process in post-event remodelling. In fact, Corsini *et al* made exactly this case, stating that the inhibition of smooth muscle cell proliferation might be clinically important. Moreover, Corsini *et al* (1996) had shown that fluvastatin inhibited smooth muscle cell proliferation in human cultured cells, and suggested that this inhibition might be important in atherosclerotic disease regression. The claim that not inhibiting smooth muscle cell growth might be beneficial was entirely conjectural. Parke Davis alleged that the Corsini *et al* (1992) reference was insufficient to support such a contentious positioning. Evidence on this subject was highly controversial and remained so.

Parke Davis noted that Clause 7.2 of the Code required claims to be objective and unambiguous and based on an up-to-date evaluation of all the evidence. The supplementary information "emerging clinical or scientific opinion" stated that "where a clinical or scientific issue exists which has not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue is treated in a balanced manner ...".

RESPONSE

Bristol-Myers Squibb and Sankyo stated that LDL-cholesterol level was an important target of cardiovascular prevention. However elevated LDL-cholesterol levels identified less than half of the individuals who would die from the consequences of atheromatous coronary artery disease. In the Lipid Research Clinics Prevalence Study (Rosenson and Tangney (1998)) LDL-cholesterol had only a 47% sensitivity in predicting 10 year coronary heart disease (CHD) death rates.

Lipostat therapy had been shown in large, landmark clinical studies, WOSCOPS (West of Scotland Coronary Prevention Study; Shepherd *et al* 1995), CARE (Sacks *et al* 1996) and LIPID, to prevent clinical cardiac events - fatal and non-fatal myocardial infarcation, CHD death and the need for coronary revascularisation - both in patients with, and without overt CHD. The evidence that supported these clinical benefits of Lipostat had been published in peer reviewed journals and presented extensively. This evidence was generally known.

The wealth of clinical data with concordant results from a number of large clinical trials in patients with and without CHD meant that Lipostat could reasonably be said to do more, clinically, than lipid modification.

In addition, in patients with CHD and average cholesterol levels, Lipostat had been demonstrated to reduce total mortality and the risk of clinical cardiac events. These findings from two large clinical trials of Lipostat in patients with CHD and average cholesterol levels were further evidence that Lipostat did more than simply lower cholesterol levels.

Bristol-Myers Squibb and Sankyo stated that there had been a widely held view for some time that the statins might do more than lower cholesterol, a view that was presented, with the supporting experimental and clinical evidence, in a Lancet review (Vaughan *et al* 1996). Since that review further analysis of the large WOSCOPS database, published in a peer reviewed journal, had led independent researchers to conclude that lipid modification alone "does not appear to account entirely for the benefits of pravastatin therapy" an observation first reported by Byington *et al* (1995) in respect of a prospective pooled analysis of earlier Lipostat studies. Those authors wrote that "... after adjustment for LDL-cholesterol reduction the treatment group effect was still statistically significant. This finding suggests that [Lipostat] may have an effect beyond simple lipid lowering". Analysis of the large CARE database (Sacks *et al* 1998) further supported these findings. The authors stated that "This left 33% of the total effect unaccounted for by the LDL concentration ...".

The size of these databases permitted scientifically valid post hoc analyses to be conducted. The fact that the results from three sets of observation were concordant compellingly supported the view that the clinical benefits seen with Lipostat were not attributable to cholesterol reduction alone.

Lipostat had been demonstrated to reduce the risk of stroke - an event for which the correlation with cholesterol levels was less certain than the link between CHD and cholesterol - further support for the premise that the clinical benefit derived from Lipostat could not be merely ascribed to Lipostat's effects on cholesterol levels and that Lipostat did more than simply lower cholesterol.

Bristol-Myers Squibb and Sankyo noted that Parke Davis had complained that there was no evidence to support the claim that Lipostat had an effect beyond simple cholesterol lowering that was not shared by other members of the statin class.

Parke Davis had acknowledged that Lipostat had effects on clinical event reduction and stated correctly, that other statins had demonstrated an effect on clinical events.

Bristol-Myers Squibb and Sankyo pointed out that:

- No other statin had demonstrated an effect on total mortality in patients with average cholesterol levels in large clinical trials.
- No other statin had demonstrated a significant reduction in clinical cardiac events in patients with CHD and average cholesterol levels.
- No other statin had been demonstrated to reduce the risk of stroke in patients with CHD and average cholesterol levels.

- No other statin had the volume of clinical event reduction data that existed for Lipostat. Post hoc analyses of the databases from these large Lipostat clinical event reduction studies were scientifically valid because of the size of the databases. These analyses consistently proved that positive benefits on death, heart attacks and stroke conferred by Lipostat therapy were not explained solely by the effect of Lipostat on cholesterol levels.

Bristol-Myers Squibb and Sankyo did not accept the complainant's view that there was no evidence to support the claim that Lipostat did more than simply lower cholesterol in a manner that was not shared by other members of the class.

Scrutiny of the SPCs for the statins currently marketed in the UK indicated that all of these agents were licensed for use in the modification of a range of lipid profiles, usually as an adjunct to diet.

In the UK Lipostat had three therapeutic indications:

- Hypercholesterolaemia
- Coronary heart disease
- Prevention of coronary heart disease

Of the agents currently available in the UK only Lipostat had been licensed by the Medicines Control Agency (MCA) for the prevention of clinical cardiac events in patients with established atheromatous coronary artery disease and to prevent the development of coronary heart disease in patients without clinically evident coronary heart disease. The Lipostat product licence was unique amongst the currently licensed statins in having these three therapeutic indications. Bristol-Myers Squibb and Sankyo considered that this authorisation reflected the wealth of the clinical data that had been presented to the MCA and permitted them to promote the claim that Lipostat did more than simply lower cholesterol, namely reduce clinical events in patients with, and at risk of, coronary heart disease. This was entirely consistent with their SPC. In fact, Parke Davis seemed to accept this in its letter to the Authority when it stated that the strapline "Lipostat offers more than just cholesterol reduction" was not untrue.

In summary Bristol-Myers Squibb and Sankyo stated that the Code did not restrict the promotion of medicines to the words used in the SPC. The Code required that promotion was consistent with the SPC and did not mislead directly or by implication. The claim that pravastatin had effects beyond simple cholesterol modification was not inconsistent with the product licence and Bristol-Myers Squibb and Sankyo did not accept that this claim lacked appropriate supporting evidence. The beneficial effects beyond simple cholesterol lowering were either not included in the SPCs of other statins, or were not supported by the wealth of clinical data, as was the case for Lipostat. Bristol-Myers Squibb and Sankyo did not accept that the claim that Lipostat offered more than cholesterol reduction in a manner that was not demonstrated for other members of the class represented a breach of the Code.

Bristol-Myers Squibb and Sankyo addressed the concern that the use of the strapline and subsequent text implied that Lipostat had special attributes in a manner which the complainant believed contravened Clause 7.2.

Bristol-Myers Squibb and Sankyo and did not accept that it was appropriate to take this text out of the intended context. The advertisement, taken as a whole, was designed to convey the point that Lipostat reduced the risk of clinical cardiac events and this benefit, as Parke Davis seemed to agree, meant that Lipostat offered more than just cholesterol reduction. When read in the setting of the entire advertisement they did not accept that the strapline, which the complainant asserted to be inherently true, breached Clause 7.2 of the Code.

Bristol-Myers Squibb and Sankyo agreed with Parke Davis that, with respect to the inhibition of platelet thrombus formation and inhibition of smooth muscle cell proliferation, the data presented was not representative of all of the currently licensed statins and that there was data to show that different statins had been demonstrated to have differential effects on properties other than cholesterol lowering, so called "pleiotropic effects".

When viewed in the context of this advertisement as a whole, the data on the pleiotropic effects of Lipostat were clearly presented in order to explain why Lipostat, which had been consistently demonstrated in large clinical trials to reduce clinical cardiac events, did so at a level that was greater than could be predicted based on lipid modification alone. These data served to illustrate that, for these key factors in the development and progression of CHD, Lipostat had effects which most would consider to be important.

Bristol-Myers Squibb and Sankyo did not accept that these data were presented in a manner which contravened the Code.

There had been a widely held view for some time that the statins might do more than lower cholesterol, a view that was posited in a 1996 Lancet review. With respect to Lipostat the data to support this view was not as limited as Parke Davis erroneously stated. There were a number of consistent reports of the effect of Lipostat on platelet thrombus formation, results which had not been consistently seen with other licensed statins.

Bristol-Myers Squibb and Sankyo noted that the findings of Corsini *et al* (1992), which had compared the effect of simvastatin and Lipostat on smooth muscle proliferation, had been supported by Nègre-Aminou *et al* (1997). A recent review article in the Journal of the American Medical Association (JAMA) stated that in both *in vitro* and *in vivo* experiments pravastatin was the only statin that did not either inhibit intimal proliferation or smooth muscle cell proliferation (Rosenson *et al* 1998). The authors stated that these effects were not seen with any of the other statins currently marketed in the UK. Bristol-Myers Squibb and Sankyo did not therefore accept that the data was "limited". They did not accept that the presentation of the data on the actions of pravastatin in the advertisement represented a breach of the Code.

Bristol-Myers Squibb and Sankyo stated that Lipostat therapy had been shown, in large clinical event studies, to prevent clinical cardiac events in patients with established atheromatous coronary artery disease and to prevent the development of coronary heart disease in patients without

clinically evident coronary heart disease. Lipostat therefore could reasonably be said to do more, clinically, than lipid modification.

In addition in patients with CHD and average cholesterol levels Lipostat had been demonstrated to reduce total mortality and the risk of clinical cardiac events and stroke.

Furthermore, independent researchers had published analyses of the large clinical event studies and concluded that lipid modification alone "does not appear to account entirely for the benefits of pravastatin therapy".

Pravastatin, at therapeutically relevant concentrations, had been shown to reduce platelet thrombus formation and did not inhibit smooth muscle cell proliferation - both important in preventing the progression of CHD or preventing CHD events.

Further, a four year prospective study in primates had demonstrated that pravastatin conferred benefits consistent with atheromatous plaque stability in a manner that was independent of the cholesterol lowering effects of pravastatin.

Bristol-Myers Squibb and Sankyo stated that if pravastatin did not have a unique, proven and licensed benefit in preventing the development and progression of CHD and in reducing CHD events, or if these benefits could be solely attributed to lipid modification, then it might be fair to say that effects on platelet thrombus formation or smooth muscle cell proliferation were of mechanistic or academic interest only.

However, the demonstrated clinical benefits seen in patients with raised and average cholesterol levels, and the fact that these benefits were greater than those predicted by lipid modification alone, added importance to the *in vitro* and *ex vivo* data on these pleiotropic effects of Lipostat. These data served to explain how the clinical event reductions seen with Lipostat, particularly those benefits that could not be explained by lipid modification alone, might be accrued and were of clinical relevance. These data were of direct clinical relevance and were presented in a manner which did not breach Clause 7.2 of the Code.

Bristol-Myers Squibb and Sankyo noted that Parke Davis had expressed a concern that inhibition of smooth muscle cell proliferation was seen by some in the scientific community as a benefit and that they had failed to fully present the scientific arguments. Parke Davis had cited the 1992 Corsini paper in support of its contention that smooth muscle cell proliferation was a benefit.

Bristol-Myers Squibb and Sankyo stated that the Corsini paper was cited in the advertisement because it presented the evidence that Lipostat, when compared with simvastatin, did not inhibit the proliferation of smooth muscle cells. A more recent study and a recent review of the area further supported this view. Bristol-Myers Squibb and Sankyo agreed with the complainant that the Corsini paper alone was insufficient to support a view that inhibition of smooth muscle cell proliferation was clinically beneficial - a view which Parke Davis believed to be "contentious" and "conjectural".

In the complaint it was correctly stated that Corsini *et al* did refer to the possible clinical benefit of inhibiting smooth muscle cell proliferation. However, Bristol-Myers Squibb and Sankyo noted that in this respect the author was writing about the development of restenosis after iatrogenic vascular injury (post percutaneous transluminal coronary angioplasty, coronary artery bypass grafting and cardiac transplantation). In relation to the development and progression of coronary artery disease and the development of clinical cardiac events - the context in which any discussion about pravastatin promotion must be viewed - Bristol-Myers Squibb and Sankyo believed that there was greater unanimity about the importance of having adequate smooth muscle cells in the atheromatous plaque than the complainant suggested. Brown *et al* (1993) described a key determinant of a plaque's vulnerability being "the fibrous cap thinned and weakened by the lack of smooth muscle cells and lysis of collagen". Libby (1995) pointed out that the smooth muscle cells were the "Guardian of the Integrity of the Plaque's Fibrous Cap". Libby went on to point out that "... those embarking on therapeutic quests seeking inhibitors of smooth muscle cell proliferation as treatments for atherosclerosis ..." should be cognisant that "Inhibition of smooth muscle cell proliferation in human patients might produce the undesired effect of destabilising vulnerable regions of atherosclerotic plaques ...". Weissberg *et al* (1996) wrote that vascular smooth muscle cells were "desirable and necessary to prevent and suppress acute coronary syndromes". Rosenson *et al* (1998), in a review of the literature published in JAMA, wrote that the smooth muscle cell fostered, through a number of mechanisms, plaque stabilisation and was involved in the healing process after plaque rupture. The authors concluded that "the permissive effect of pravastatin [Lipostat] on smooth muscle cell proliferation might be an advantage for the reparative process that follows plaque ulceration". The presentation of the smooth muscle cell proliferation data was entirely consistent with current scientific thinking and had been presented in a factual clear and balanced manner. Bristol-Myers Squibb and Sankyo did not accept that the data had been presented in a manner that breached the Code.

PANEL RULING

The Panel noted that the strapline "Lipostat offers more than just cholesterol reduction" was supported by the references provided. The strapline was accurate and not inconsistent with the Lipostat SPC. In the opinion of the Panel, however, the statement "Lipostat also goes beyond class effect, reducing platelet thrombus formation and not inhibiting the proliferation of smooth muscle cells - both important factors in coronary heart disease", in conjunction with the strapline conveyed the impression that the reduction of platelet thrombus formation and the lack of inhibition of the proliferation of smooth muscle cells were benefits beyond lipid modification not shared by other statins.

The statement was referenced to two studies which compared simvastatin and pravastatin only, Corsini *et al* (1992) and Lacoste *et al* (1996). The Panel noted that Bristol-Myers Squibb and Sankyo had acknowledged that this data was not representative of all the currently licensed statins and that there was other data to show that different statins had differential effects on properties other than cholesterol lowering.

The Panel noted that the data supporting the effect of pravastatin on smooth muscle proliferation was from *in vitro* studies. The supplementary information to Clause 7.2 of the Code stated that "Care should be taken with the use of such data so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there is data to show that it is of direct relevance and significance". The Panel noted that whilst the reduction of platelet thrombus formation and non-inhibition of the proliferation of smooth muscle cells had been suggested as factors in coronary heart disease their significance in terms of therapeutic outcome was not known.

The Panel considered that the advertisement overstated the totality of the data and was misleading in breach of Clause 7.2 of the Code.

APPEAL BY BRISTOL-MYERS SQUIBB AND SANKYO

The respondent companies appealed the ruling of a breach of Clause 7.2 of the Code. As some of the issues involved were common to both allegations the reasons for the appeal are set out in point 2 below.

2 Brochure

COMPLAINT

Parke Davis stated that the brochure had only just come to its attention and was distributed to healthcare professionals attending an International Congress on Vascular Disease Prevention meeting in Glasgow. The brochure took the same promotional stance as the advertisement. It was not even clear from the brochure whether patients might be expected to benefit in some way from the lack of change in smooth muscle cell proliferation. By its very inclusion Bristol-Myers Squibb and Sankyo implied a benefit but they did not provide any meaningful extrapolation. Notwithstanding this, any implication of benefit would be contrary to scientific evidence in an area where there was no consensus. Parke Davis alleged that it was therefore misleading and in breach of Clause 7.2.

Parke Davis stated that additionally, page 4 of the brochure implied "extra pravastatin benefits" based on a post hoc subgroup analysis from the WOSCOP study. The page illustrated a 36% coronary event risk reduction in patients whose cholesterol was reduced to a specific level as compared with those patients taking placebo who were at this level without any lipid lowering therapy. The brochure claimed this effect was a special attribute of pravastatin over and above its lipid modifying effect. However, the study itself hypothesised primarily that it was a reduction in LDL-cholesterol rather than an absolute cholesterol value that had influenced the outcome and not necessarily some special attribute of pravastatin. In any event, a number of effects beyond cholesterol reduction had been seen with other statins, although, as with pravastatin, their significance in terms of therapeutic outcome was not known. Parke Davis alleged that it was inappropriate and in breach of Clause 7.2 of the Code to make claims implying that there was some special attribute of pravastatin based on such limited data. The WOSCOP study was not designed to measure the effects of pravastatin on these parameters and did not give any credence to any such purported clinical benefit associated with these parameters.

Parke Davis also pointed out that the brochure contained no reference to where prescribing information could be found and was therefore in breach of Clause 4.6 of the Code.

Parke Davis was particularly concerned that this promotional item was distributed at an international meeting after Bristol-Myers Squibb and Sankyo had received a warning letter from the Division of Drug Marketing, Advertising and Communication (part of the FDA) regarding this very position of promotion for Lipostat in the USA. Parke Davis had referred this matter to its US colleagues for their action.

RESPONSE

Bristol-Myers Squibb and Sankyo stated that the brochure was a complete item and must be viewed as a whole. With regard to the data on smooth muscle cell proliferation the companies noted that the brochure was designed to make the point that pravastatin had been demonstrated to offer protection from clinical events to patients with coronary heart disease, and at risk of coronary heart disease , and that further analyses of these large clinical trial databases showed that the protection afforded by Lipostat was greater than might be predicted by lipid modification alone. The brochure presented data from experiments that served to explain some of the mechanisms by which this additional benefit was attained. These mechanisms included the effects of Lipostat on platelet thrombus formation and smooth muscle cell proliferation.

It was in this context that the data in question was presented and should be viewed. The data was presented in a truthful and fair manner and were clearly part of the total piece included in order to explain how some of the licensed, and unlicensed, clinical benefits seen in large studies with pravastatin might be accrued.

Bristol-Myers Squibb and Sankyo did not agree with the complainant about the clinical importance of inhibition of smooth muscle cell proliferation and referred to their comments at point 1 above.

Bristol-Myers Squibb and Sankyo addressed the allegation that the presentation on page 4 of the brochure of post hoc analyses from the WOSCOPS database implied a "special attribute" of pravastatin over and above its lipid modifying effect and that it was inappropriate to do so based on "such limited data".

The data presented were from one of a number of similar analyses conducted by the independent researchers, Packard *et al* for the WOSCOP Group and were the results of a post hoc analysis from a large clinical trial of Lipostat in patients without evident coronary heart disease. These data had been published in a peer reviewed journal and had been correctly cited in the promotional brochure. Based on these analyses Packard *et al* concluded that lipid modification alone "does not appear to account entirely for the benefit of pravastatin therapy".

Bristol-Myers Squibb and Sankyo considered that the data presented was an accurate presentation of the facts about the medicine, there were further analyses from other landmark studies which supported the data.

Bristol-Myers Squibb and Sankyo did not consider that this page should be viewed in isolation, the piece as a whole clearly conveyed the message that Lipostat protected patients from clinical events, that it did so in a way that could not be fully explained by lipid modification alone, and the piece provided some mechanistic explanation for these non-lipid related benefits.

Bristol-Myers Squibb and Sankyo agreed with the complainant that there was data to show that different statins had been demonstrated to have differential effects on properties other than cholesterol lowering. They also agreed that the clinical relevance of these different properties had not been explained in terms of therapeutic outcome for all of the agents in the class. Bristol-Myers Squibb and Sankyo referred to their response at point 1 above, in which the therapeutic relevance of these data for Lipostat was explained.

Bristol-Myers Squibb and Sankyo submitted that all of the data was presented in a manner which was accurate and fair and they did not consider that there was any breach of the Code.

With regard to the allegation that no reference was made as to where prescribing information could be found, Bristol-Myers Squibb and Sankyo submitted that the brochure was prepared for, and distributed at, an international meeting held in the UK. The brochure referred to the unlicensed indication of stroke and was certified as a truthful and fair presentation of the facts about Lipostat. The fact that the brochure did not state where the prescribing information could be found did not represent a breach of the UK Code. The prescribing information occupied a large part of the back page of the brochure.

PANEL RULING

The Panel noted that pages 5 and 6 of the brochure made claims about pravastatin and the reduction of platelet thrombus formation. On page 7 of the brochure, headed "Stable plaques decrease the risk of heart attacks", claims were made about the role of smooth muscle cells in the protection and stability of plaques. The following page was headed "Pravastatin does not inhibit smooth muscle cell proliferation" and subsequent data showed that smooth muscle cell was inhibited by simvastatin and fluvastatin. Page 9 of the brochure was subtitled "Mechanisms that may explain pravastatin's additional benefits" and contained a flow chart which showed two alternative mechanisms whereby pravastatin might reduce the risk of coronary heart disease. The first pathway was via lipid modification and cholesterol reduction. The second pathway was via ancillary mechanisms which reduced platelet thrombus formation and did not inhibit smooth muscle cell proliferation. A footnote to the second pathway stated that this data was from *in vitro* studies.

The Panel considered that its ruling at point 1 applied here with regard to the data on smooth muscle cell proliferation. The Panel therefore ruled a breach of Clause 7.2 of the Code.

The Panel examined page 4 of the brochure. The paper published by the West of Scotland Coronary Prevention Study Group (1998) was a post-hoc analysis of data derived from a placebo controlled trial to measure the effectiveness of pravastatin in reducing morbidity and mortality from coronary heart disease in mildly hypercholesterolaemic men. The 1998 WOSCOP study stated that in an exploratory analysis it was observed that in subjects with the same mean LDL-cholesterol those receiving pravastatin had a lower CHD risk than those receiving placebo. Several theoretical reasons for this difference were discussed. The authors warned that the results described were derived from post hoc analysis and therefore must be viewed cautiously. Nevertheless the results indicated that the benefit seen with pravastatin treatment, although obviously linked to a decrease in LDL, could not be explained by this alone.

The Panel noted that other statins had exhibited differential effects other than cholesterol lowering. Given the reservation expressed in the study, that the data be viewed with caution, the Panel considered the page prominently detailing such data was misleading and insufficiently qualified. A breach of Clause 7.2 of the Code was ruled.

The SPC stated that pravastatin was licensed for the treatment of hypercholesterolaemia, coronary heart disease and prevention of coronary heart disease in the UK. The Panel noted that pravastatin was licensed for prevention of stroke in the USA and several European countries, excluding the UK.

The Panel noted that indications for pravastatin which were licensed in the UK, other than stroke, were mentioned in the brochure. The requirements set out in the supplementary information to Clause 3 of the Code referred to promotional material for medicines and indications which did not have a UK marketing authorization. The brochure promoted indications which were licensed in the UK and hence, in the Panel's view, had to comply with all relevant requirements of the Code. The brochure consisted of more than four pages and therefore needed a reference as to where the prescribing information could be found. The Panel ruled a breach of Clause 4.6 of the Code.

APPEAL BY BRISTOL-MYERS SQUIBB AND SANKYO

Bristol-Myers Squibb and Sankyo appealed all of the breaches ruled by the Panel. Information was presented to demonstrate that:

the class effect of the statins was cholesterol lowering; the clinical benefits observed with Lipostat could not be fully explained by cholesterol lowering; the presentation of the possible mechanisms to explain these non-cholesterol effects was not misleading.

In support the companies provided submissions from professors who were two of the principal authors of the WOSCOP study. These submissions emphasised the validity and clinical relevance of the non-cholesterol lowering Lipostat.

One of the two professors submitted the following:

The complaint seemed to be that the benefits of pravastatin over and above its lipid modifying effect were a special attribute of pravastatin. That might or might not be the case. However, no such claim was made in the WOSCOPS publication in Circulation referenced on page 4 of the brochure, nor was any such claim made on page 4 itself. All that was stated was that the total benefits of pravastatin did not appear to be attributable to lipid modification alone.

The professor noted that a second point made in the complaint was that the WOSCOPS analysis was not prespecified. It was true that prior to the conduct of the study the primary hypothesis was that the benefits of pravastatin treatment would come primarily from a reduction in LDL cholesterol with some additional benefit from changes in HDL cholesterol and triglycerides. The investigators did prespecify an analysis relating changes in LDL to outcome. However, over the 7 year study period, science moved on. The event reduction analysis was motivated mainly by evolving evidence from animal and other studies that statin treatment might involve more than LDL cholesterol lowering. Hence, although many details of analyses were not pre-specified before the study started in 1988, they were a clear and natural response to evolving scientific theories about the potential non LDL effects of the statins. In that sense, the professor considered the WOSCOPS event reduction analysis as being supportive of these evolving theories and hence an important part of the jigsaw which was currently being put together to provide a clearer understanding of the mechanisms for the benefits which medicines such as pravastatin provided. In presenting this body of evidence to doctors it was vital that key sections of the jigsaw were not omitted.

The professor noted that the analysis presented on page 4 of the brochure was supported by a further analysis, in a paper published in Circulation, which suggested that based on achieved levels of total cholesterol and HDL cholesterol the Framingham risk model accurately predicted CHD event rates in the placebo group but overestimated rates in the pravastatin group. The statistical methods used by the WOSCOPS group in the paper published in Circulation were uncontroversial and did not even draw comment from the journal's statistical reviewer. It was true that all results which were not drawn from randomised comparisons had to be treated with caution. However, the investigators' analyses produced similar conclusions with two different analysis strategies and results which fitted in with previous and recent mechanistic research.

The other professor submitted the following:

General overview: Prospects for prevention of coronary disease had improved dramatically over the last few years with the publication of 5 major statin-based outcome trials (4S, WOSCOPS, CARE, LIPID and AFCAPS). Previous studies with other lipid-lowering medicines revealed some benefit of therapy (as in the LRC-CPPT and HHS) but they were far from convincing. Even the recently announced BIP trial (with bezafibrate) had proved to be a disappointment. It was Michael Oliver who proclaimed in the British Medical Journal that "Statins prevent coronary heart disease" and commented, as the authors of WOSCOPS did in their main paper, on the surprising early benefit seen in the study which did not fit with the paradigm of slow regression of lesions leading to less clinical events. The authors understood that plaque stabilisation was the major change in arterial lesions that produced fewer myocardial infarctions and were striving to understand the mechanisms that generated this effect.

The professor stated that it was now widely accepted that the key feature of an unstable atherosclerotic plaque was not its size, which was thought to be linearly related to LDL levels in the blood, but the stability of the plaque cap. The determinants of cap stability were unknown. A high LDL level was likely to be important but so was increased blood pressure, the presence of inflammatory cells and the status of the smooth muscle cells in the locality of the lesion. One thing was clear, the changes that led to a reduced risk of myocardial infarction were complex, could not simply be derived by extrapolation from epidemiological observational studies and must be understood in light of large-scale outcome studies. The recently published HERS study was a prime example where beneficial lipid changes led, contrary to expectation, to no reduction in clinical events (Hulley *et al* 1998)

Event Reduction analysis: The professor submitted that analysis of the relationship between change in LDL level and reduction in CHD event rate had assumed a greater significance than it was first accorded since, as noted above, the paradigm by which it was understood what led to a myocardial infarction altered dramatically between the time the major statin trials were designed and their publication. In the WOSCOPS design paper in 1992 the investigators stated that they would examine the relationship between LDL change on pravastatin and CHD reduction using a specific statistical test. Therefore, this was a pre-specified, not post-hoc analysis. Contrary to expectation, no clear linear graded association was seen even though there was the statistical power to detect one. In further analyses the investigators found (as did CARE and 4S) that the association between fall in LDL and CHD reduction was curvilinear or possibly even exhibited a threshold. Thus, the widely held belief that "lower LDL is automatically better" was challenged by data from these key studies. Since the fall in LDL in a pre-specified analysis did not predict the decrease in risk the investigators explored the possibility that the benefit of treatment was not fully explained by the achieved LDL level. This was done in two ways. First, using an epidemiologically derived equation it was calculated that the CHD risk reduction should have been 24% instead of the 35% observed. Second, in subjects matched for LDL levels in the two treatment arms of the study, those receiving pravastatin appeared to have a lower risk than those on placebo. (The basis of page 4 of the brochure and the advertisement). In discussing these results the investigators were cautious but concluded that the benefits of treatment could not be explained by the LDL reduction only. "Cautious" did not mean the findings, even though derived in part from post-hoc analysis, should be dismissed, rather that they be viewed thoughtfully in light of the changing understanding of the nature of a myocardial infarction (as described above).

Non-Lipid mechanisms of benefit: The professor stated that the finding of unexpected early benefit of statin therapy in trials like WOSCOPS, a lack of a linear

relationship between LDL reduction and risk reduction and the change in the paradigm describing an acute coronary event had led to the widespread belief (among opinion leaders up-to-date with the literature) that medicines with proven clinical benefit could not be judged solely on the basis of their ability to lower LDL cholesterol. This conclusion was highlighted by the recent publication from the CARE trial in which it was shown that the high risk associated with a pro-inflammatory state was attenuated by pravastatin treatment, an effect that could not be linked to variation in lipid levels. The authors concluded that this was "an observation consistent with a non-lipid effect of this agent" (Ridker *et al* 1998).

The professor stated that if in light of the above it was accepted that all lipid modifying agents could not be judged on the basis of "simple cholesterol lowering" then if the discussion was narrowed down to the statin class were these all likely to behave in the same way? A recent review had summarised thinking on this topic in some detail (Rosenson and Torgney 1998). In a number of *in vitro* and *ex vivo* systems and in animal models it was clear that due to structural differences the individual drugs exhibited different properties, eg in preventing thrombus formation, inhibiting smooth muscle cell proliferation or lowering plasma viscosity (WOSCOPS, unpublished observation). Rosenson concluded "Since the non-lipid properties of statins differ despite comparable LDL cholesterol lowering, the net clinical efficacy of these agents requires validation by randomised clinical trials".

In conclusion the professor stated that it seemed reasonable at this point in time to inform physicians of the event reduction data from clinical trials to make them aware of the discordancy between extent of LDL reduction and degree of risk reduction. If LDL change could not be shown to be the sole determinant of benefit and other mechanisms appeared to contribute then this too should be brought to their attention.

The companies also appealed against the Panel's ruling of a breach of 4.6 of the Code with regard to the brochure. It was noted that the supplementary information to Clause 3 of the Code "Promotion at International Conferences" stated that any promotional material for medicines or for indications which do not have a UK marketing authorization must be clearly and prominently labelled as such" and that signatories should "..... certify only that in their belief the material is a fair and truthful presentation of the facts about the medicine." The companies stated that as the brochure was predominantly about stroke, which was an unlicensed indication for Lipostat, the supplementary information quoted above applied and so the material only needed to be fair and truthful. In such an instance Clauses 4.6 and 7.2 did not apply.

APPEAL BOARD RULING

1 Journal Advertisement

The Appeal Board noted the statement at issue in the journal advertisement that "Lipostat also goes beyond class effect reducing platelet thrombus formation and not inhibiting the proliferation of smooth muscle cells - both important factors in coronary heart disease." The Appeal Board considered that the precise meaning of the phrase "class effect" was unclear although in the Appeal Board's view most readers would assume it meant cholesterol lowering. The Appeal Board noted that while pravastatin did more than lower cholesterol in patients with raised cholesterol levels there was data to show that other statins also had effects other than cholesterol lowering. The Appeal Board noted that the data to support the effect of pravastatin on smooth muscle cell proliferation was from *in vitro* studies. The Appeal Board noted that whilst the reduction of platelet thrombus formation and non-inhibition of the proliferation of smooth muscle cells had been suggested as factors in coronary heart disease their clinical significance was not known.

The Appeal Board considered that the advertisement overstated the totality of the data and was misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal on this point was unsuccessful.

2 Brochure

The Appeal Board examined the brochure and noted that it discussed indications for pravastatin which were licensed in the UK and contained the UK prescribing information. The brochure also contained information about stroke which was not a licensed indication in the UK. The Appeal Board considered that, notwithstanding the inclusion of information about stroke, as the brochure discussed UK licensed indications it needed to comply with the whole of the Code. It did not come within the exemption in the supplementary information to Clause 3 of the Code such that it need only be certified to be a fair and truthful presentation of the facts about the medicine. Only the section detailing the use of pravastatin in stroke could claim the exemption granted in the supplementary information to Clause 3. The brochure should have included a reference as to where the prescribing information could be found. The Appeal Board upheld the Panel's ruling of a breach of Clause 4.6 of the Code.

The appeal on this point was unsuccessful.

The Appeal Board considered that with regard to the effect of pravastatin on platelet thrombus formation and smooth muscle cell proliferation its ruling of a breach of Clause 7.2 of the Code in point 1 above also applied here.

The appeal on this point was unsuccessful.

The Appeal Board examined page four of the brochure which was headed "Pravastatin - more protection than expected" and gave detailed results from WOSCOPS. The claim that the benefits of pravastatin were not attributable to lipid modification alone was an accurate reflection of the WOSCOPS data. The Appeal Board did not consider that the page was misleading and insufficiently qualified. The Appeal Board upheld the appeal on this point and ruled no breach of Clause 7.2 of the Code.

The appeal on this point was successful.

Complaint received **29 May 1998**

Case completed **19 November 1998**

CASE AUTH/728/6/98

GLAXO WELLCOME v ASTRA

Oxis Turbohaler 12 hospital dosage card

Glaxo Wellcome complained about an Oxis Turbohaler 12 (eformoterol) hospital dosage card issued by Astra, alleging that the claim "A significant advance in asthma management" was not capable of substantiation and did not reflect the evidence clearly and was therefore misleading in breach of the Code. Beneath the claim were four bullet points which Glaxo Wellcome commented on in turn. One, "The only long- acting bronchodilator to have demonstrated 12 month outcome benefits" had already been ruled in breach in a separate case, the others "Significantly reduces severe and mild asthma attacks in addition to high or low dose steroid", "Significantly reduces the need for rescue medication compared to steroid alone" and "Demonstrated not to cause underlying deterioration in asthma over a 12 month period" were not considered by Glaxo Wellcome to amount to a significant advance.

The Panel noted, but did not accept, Astra's submission that the claim referred to the Oxis Turbohaler and the importance of the FACET study, and its results as a whole, in relation to asthma management. Neither the claim in question nor the four bullet points mentioned the FACET study although the bullet points were referenced to it. The Panel accepted that the FACET study had established important clinical results with Oxis but did not consider that Oxis had significantly changed asthma management. In the Panel's view the claim was misleading with regard to the impact of Oxis on the management of asthma and a breach of the Code was ruled.

Upon appeal by Astra, the Appeal Board considered that the claim "A significant advance in asthma management" was a claim for the product Oxis Turbohaler 12 and not a claim relating to the impact of the FACET study. The Appeal Board acknowledged that the results of the FACET study were important with regard to the management of asthma and the use of Oxis Turbohaler 12, but noted that the authors had concluded that their results supported existing therapeutic guidelines that recommended the addition of a long-acting beta-agonist to low doses of inhaled steroids. In the Appeal Board's view, the results of the FACET study did not justify the claim regarding the impact of Oxis Turbohaler 12 on the management of asthma. The Appeal Board upheld the Panel's ruling that the claim was misleading in breach of the Code.

This complaint concerned a hospital dosage card (ref OXIS 97 2449) for Oxis Turbohaler 12 (eformoterol) which had been issued by Astra Pharmaceuticals Ltd. Glaxo Wellcome UK Limited had previously alleged, in Case AUTH/694/4/98, that the claim "A significant advance in asthma management" was a hanging comparison but that allegation had been rejected by the Panel. Glaxo Wellcome accepted the ruling but had made a new allegation in relation to the same claim. The matter was dealt with as a fresh complaint. The claim appeared in bold as the main heading. Four bullet points, in a lesser type size, below the heading made clinical claims for the Oxis Turbohaler 12 derived from the results of the FACET study.

COMPLAINT

Glaxo Wellcome alleged that the claim was not capable of substantiation and did not reflect the evidence clearly. It was therefore misleading and in breach of Clause 7.2 of the Code. Glaxo Wellcome commented in turn on the four bullet points.

a) "The only long-acting bronchodilator to have demonstrated 12 month outcome benefits"

Glaxo Wellcome pointed out that this had already been ruled to be in breach as salmeterol had 12 month outcome benefits [Case AUTH/694/4/98]. Oxis could therefore not be said to be a significant advance in asthma management on this account.

b) "Significantly reduces severe and mild asthma attacks in addition to high or low dose steroid"

Glaxo Wellcome stated that while the FACET study would appear to have been the first study set up with primary outcome measures being exacerbation rates, nevertheless there was data on salmeterol showing exacerbations were reduced. The six months' study by Ind *et al* (in 1998) showed reductions in moderate and severe exacerbations in all groups examined and, in particular, the group on the combination of inhaled steroid and long-acting bronchodilator showed greater reduction in severe exacerbations than the group on higher dose inhaled steroid alone. Indeed, in 1997 this was presented as preliminary information in the same session of the European Respiratory Society as the FACET data so Astra should have been aware of this information. Taylor *et al* (1997) compared the addition of salmeterol with regular salbutamol in mild to moderate asthmatics and again showed in this six month study a significant reduction in exacerbation rates (p=0.009) compared to placebo. The addition of salbutamol had no significant effect to placebo. Glaxo Wellcome suggested therefore, that as this data had been available now for a year, albeit in studies of six months' duration, Oxis did not represent a significant advance in this respect either.

c) "Significantly reduces the need for rescue medication compared to steroid alone"

Glaxo Wellcome stated that the need for rescue medication was one of the commonly reported secondary outcome measures in many clinical trials that had been undertaken with salmeterol. In many of these there was significant reduction in the amount of rescue medication used compared to placebo. Glaxo Wellcome would be prepared to give a comprehensive list of supporting references, which would be considerable, but examples that should be well known to Astra were provided. Glaxo Wellcome submitted therefore that salmeterol had for many years been shown to reduce significantly the need

for rescue medication compared to steroid alone, so that for Astra to show this was also true of Oxis did not represent a "significant advance".

d) "Demonstrated not to cause underlying deterioration in asthma over a 12 month period"

Glaxo Wellcome stated that Lundbeck *et al* (1993) and Britten *et al* (1992) looked at withdrawals in the 12 months' safety aspect of these two important trials. Neither study showed significant deterioration in asthma in the group that had salmeterol added compared to regular salbutamol. These were not even compared to higher dose inhaled steroid and therefore it was difficult to justify how Oxis could be seen to be a significant advance in this particular respect.

RESPONSE

Astra stated that whilst it would comment on the four bullet points to which Glaxo Wellcome referred, it should be understood that the use of the claim referred to Oxis Turbohaler and the importance of the FACET study, and its results as a whole, in relation to asthma management. The importance of the FACET study design, the key asthma management questions it set out to answer and the results demonstrated with Oxis Turbohaler had received widespread clinical acceptance since its publication in the New England Journal of Medicine. As a result Astra believed that Oxis Turbohaler and the FACET study did constitute a significant advance in asthma management.

With regard to the four bullet points in Glaxo Wellcome's complaint:

a) "The only long-acting bronchodilator to have demonstrated 12 month outcome benefits"

Astra referred to Case AUTH/694/4/98 which had established that, with appropriate qualification, the claim could be made that Oxis was "the only long-acting bronchodilator to have demonstrated 12 month outcome benefits".

The qualifications which accompanied such a claim were:

- Oxis was the only long acting bronchodilator which had demonstrated a significant reduction in both severe and mild exacerbations of asthma in addition to both high and low dose steroid over a full 12 months. Furthermore, this data was compared to placebo in both high and low dose steroid arms so that the true benefit of the addition of Oxis could be clearly assessed over the twelve month period.

- Oxis was the only long acting bronchodilator that had demonstrated a reduction in rescue medication in asthma when its addition to both high and low dose steroid treatment groups, in comparison to placebo, was assessed over a full 12 month period.

As stated in Case AUTH/694/4/98, Astra did not disagree that 12 month data existed for salmeterol. However the above mentioned specific 12 month outcome data was unique to Oxis and therefore it was acceptable to make such a claim when qualified appropriately.

b) "Significantly reduces severe and mild asthma attacks in addition to high or low dose steroid"

The FACET trial clearly showed over 12 months that Oxis, in addition to either high or low dose steroid, was able to demonstrate a significant reduction in both mild and severe exacerbation rates.

In the abstract by Ind *et al* (1998) the main results were presented in a tabular form comparing the addition of salmeterol to low dose steroid with the pre-trial exacerbation rates. The authors stated that severe exacerbations were significantly reduced by salmeterol added to low dose steroid compared to the low dose steroid alone, however it was not clear whether this was between treatment groups or compared to pre-trial levels. Even if this referred to between treatment groups the only comparison was between low dose steroid plus salmeterol and low dose steroid alone over a six month period (and with very small exacerbation rates in both groups as emphasised by the authors).

The results, in addition, clearly showed that the effect of steroid alone was highly effective, with or without salmeterol, in reducing exacerbations. Unlike the FACET study, no results were presented comparing the differences between exacerbation rates in the high dose steroid treatment group and a salmeterol/high dose steroid treatment group. There were no data presented for a full 12 month period and there was no placebo control in this study.

The abstract by Taylor *et al* (1997) looked at the effects of salmeterol vs regular salbutamol or placebo. There was no reference to steroid dose in any of the patients, indeed it was not even clear whether they received inhaled corticosteroids. As such, no definitive conclusions could be drawn from the results in relation to the benefits, in terms of exacerbation reduction, of giving salmeterol to patients on different doses of inhaled steroids.

Neither of these studies specifically demonstrated a significant reduction in severe and mild exacerbations in addition to high or low dose steroids, compared with placebo as demonstrated over twelve months in FACET. As a result of the trial design, the 12 month duration and robust results, Oxis and the FACET study did represent a significant advance for asthma management.

c) "Significantly reduces the need for rescue medication compared to steroid alone"

Astra accepted that the use of rescue medication was one of the commonly reported secondary outcome measures in many clinical trials in asthma. It also accepted that reduction in rescue medication had been demonstrated previously. However, the important point was that such a reduction in rescue medication had not been shown previously for a long acting bronchodilator:

- over a full 12 month period in such a well defined patient population
- compared with placebo in all treatment groups
- in addition to both high and low dose steroids.

These findings had been demonstrated clearly in the FACET study. As a result such data for Oxis constituted an important advance for the management of asthma patients.

d) "Demonstrated not to cause underlying deterioration in asthma over a 12 month period"

As the Panel noted in its previous ruling (Case AUTH/694/4/98) there were differences between the Britton *et al*, Lundbeck *et al* studies and the FACET study. In view of the nature of the design of the FACET study and the fact that it continued in one mode for a full twelve months, it provided important information on the control of the underlying asthma in patients on fixed doses of steroids. This did constitute a significant advance, as the use of regular, long-acting bronchodilators, in addition to inhaled steroids, had been an area of concern for respiratory physicians. Because the steroid was controlled throughout the twelve months, any "detrimental" effect could be clearly assessed. Importantly, the results showed the converse: with the addition of Oxis Turbohaler, using exacerbations as a measure of underlying asthma control, patients with Oxis actually did better than those on inhaled steroid alone. This had not been demonstrated previously over twelve months with long acting bronchodilators.

Lundbeck *et al* and Britton *et al* had presented 12 month data on salmeterol. In both cases the trials consisted of a 3 month period of close observation measuring lung function and symptoms followed by a 9 month extension for the collection of safety data. The dosage of inhaled steroids/additional therapies was not clearly defined or controlled (indeed 40% of patients in the Lundbeck study did not receive steroids at all) or placebo arms included in either study. As such the nature of the trial designs and the parameters measured in the treatment groups did not answer the questions which FACET set out to answer and demonstrated clearly in patients controlled on inhaled steroids. Indeed as discussed above the FACET study actually demonstrated that with Oxis there was additional benefit in controlling asthma - this was not shown in the Lundbeck and Britton trials.

In summary, Astra believed that Oxis Turbohaler, as a result of the FACET study design and results demonstrated, did represent a significant advance in asthma management. The FACET study had been received very positively since its publication in view of the key questions in asthma management it set out to answer (as detailed in Case AUTH/694/4/98), as well as the important results demonstrated with Oxis Turbohaler.

Astra believed it had provided appropriate clarification on the issues raised by the complainant. It denied any breach of the Code, in particular in relation to the requirements of Clause 7.2.

PANEL RULING

The Panel noted that Astra was concerned that the Authority had accepted a fresh complaint from Glaxo Wellcome in relation to the claim at issue after the Panel had rejected its first complaint about it. The Authority had taken the view that the second complaint should proceed as it consisted of a different allegation, albeit related to the same claim.

The Panel noted that at the top of the hospital dosage card was the heading "Introducing Oxis Turbohaler 12" underneath which was the main heading in bold "A significant advance in asthma management". The Panel noted Astra's submission that the claim referred to Oxis Turbohaler and the importance of the FACET study, and its results as a whole, in relation to asthma management. The Panel did not accept Astra's submission on this point. Neither the claim in question nor the four bullet points specifically mentioned the FACET study although the bullet points were referenced to it. The bullet points were not sufficiently qualified. The Panel noted that in Case AUTH/694/4/98 it had ruled that the first bullet point "The only long-acting bronchodilator to have demonstrated 12 month outcome benefits" was insufficiently qualified with regard to the outcome benefits and was misleading in breach of Clause 7.2 of the Code.

The Panel noted that Oxis 12 was eformoterol in a Turbohaler device. Eformoterol had been available as Foradil for some time. The Panel accepted that the FACET study had established important clinical results with regard to the use of Oxis. The Panel did not consider, however, that Oxis had significantly changed asthma management. The bullet points were not sufficient to justify the claim "A significant advance in asthma management".

In the Panel's view the claim was misleading with regard to the impact of Oxis on the management of asthma and a breach of Clause 7.2 was ruled.

APPEAL BY ASTRA

Astra considered that the use of the statement "A significant advance in asthma management", must be addressed as a whole in the context of current asthma management.

There were several key issues in relation to the use of long-acting bronchodilators in asthma, in particular:

- Long term control - it had been questioned if the regular use of a long-acting bronchodilator might mask underlying inflammation in the lungs and thus lead to deterioration of asthma over the long term.
- Treatment of patients uncontrolled on low dose inhaled corticosteroid therapy - current British Thoracic Society (BTS) Guidelines on Asthma Management suggested either adding a long-acting bronchodilator or increasing the dose of inhaled steroid, with no information as to which was better, or in which patient groups which option would be of optimum benefit.
- The use of long-acting bronchodilators in patients already receiving high dose inhaled steroids - this could be recommended if additional benefits could be demonstrated.

Astra submitted that asthma management could be assessed by measuring a number of variables of lung function, symptoms and rescue medications. While each of these could be of value, the most significant clinical outcome, apart from death, was exacerbations of asthma.

All of these issues were addressed in the FACET study.

The FACET study was specifically set up to answer three important questions in asthma management. These were:

1 Was there evidence of deterioration in asthma control with long-term use of a regular long-acting bronchodilator?

2 Which option was better in asthmatics uncontrolled on low dose inhaled steroid - to increase the dose of inhaled steroid or to add in a long-acting bronchodilator?

3 Was there further room for improvement by the addition of a long-acting bronchodilator to a high dose of inhaled steroid?

The unique design of the FACET study looking at the addition of Oxis Turbohaler to both high and low dose inhaled steroid over a full 12 month study period, allowed these important issues to be addressed.

Astra stated that the primary outcome measures assessed over the 12 months - severe and mild exacerbations of asthma - had not been used as primary variables in such a study before. The use of exacerbations as a measure of asthma control was highly relevant to physicians and patients alike. In particular, the severe exacerbations were defined by physicians in 80% of cases as needing courses of oral steroids. This clinical outcome measure, with the resultant use of oral steroid courses, was highly relevant to practising physicians and imparted more meaningful clinical information on the management of asthma than relying simply on lung function measurements.

The results of the FACET study were highly significant for the management of asthma.

The results demonstrated that, in patients controlled throughout the 12 month period on either high or low dose steroid, Oxis Turbohaler did not cause a deterioration in the control of asthma. Of greater importance, the contrary to this was shown in that, regardless of whether patients were on high or low dose inhaled steroid, there were clear benefits from the addition of Oxis Turbohaler with regard to reduction in both mild and severe exacerbation rates, use of rescue medication and symptom control over the 12 month period.

The results were of high clinical significance, as they helped address the concern about the use of regular long-acting bronchodilators in patients on regular inhaled steroid, whether high or low dose. The FACET study in addition allowed an assessment of the use of high vs low dose inhaled steroid alone. Thus the results of the study overall helped to address the issue of which management option physicians could undertake with their asthmatic patients uncontrolled on low dose inhaled steroid.

Astra stated that the FACET study used Oxis Turbohaler throughout the 12 month period. Whilst the Panel noted that eformoterol had been available as Foradil for some time, it should be pointed out that the results of FACET could not be extrapolated to eformoterol in another device. There were wide differences in the devices available for asthma management with regard to, for instance, lung deposition, efficacy, patient acceptability and compliance. The high degree of lung deposition achieved with the Turbohaler device was an important factor in determining clinical efficacy of various asthma therapies. The high lung deposition characteristics of the Turbohaler device were acknowledged in the current BTS Guidelines on Asthma Management in the context of inhaled steroid administration. In addition, it could not be assumed that the results of the FACET study could be extrapolated to a different long-acting bronchodilator. Indeed the authors of the study concluded that results of the FACET study should not be extrapolated.

Astra stated that the four stab-points outlined in the leavepiece were referenced to the FACET study and supported the claim that Oxis Turbohaler 12 was a significant advance in asthma management.

The control of patients on high and low dose inhaled steroid, the use of relevant outcome measures in the form of severe and mild exacerbations and the nature of the results demonstrated were points of clinical relevance and were clearly significant in comparison to previous evidence available for the management of asthma patients.

Astra submitted that experts in asthma considered that the FACET study, by addressing several important and previously unanswered questions about the use of a long-acting bronchodilator and inhaled corticosteroid, was of clinical significance and could result in a review of asthma management guidelines.

In conclusion Astra provided copies of letters from opinion leaders expressing their positive views on the FACET study and the use of Oxis Turbohaler in the management of asthma patients on inhaled steroid.

As the long-acting bronchodilator in the FACET study, Oxis Turbohaler 12 produced benefits not previously documented for a long-acting bronchodilator.

Astra considered that describing Oxis Turbohaler 12 as "A significant advance in asthma management" was justified and endorsed by opinion leaders in asthma. The company, therefore, denied a breach of Clause 7.2 of the Code.

APPEAL BOARD RULING

The Appeal Board considered that the claim "A significant advance in asthma management" was a claim for the product Oxis Turbohaler 12 and not a claim relating to the impact of the FACET study.

The Appeal Board acknowledged that the results of the FACET study were important with regard to the management of asthma and the use of Oxis Turbohaler 12 but noted that the authors had concluded that their results supported existing therapeutic guidelines that recommended the addition of a long-acting beta-agonist to low doses of inhaled steroids.

In the Appeal Board's view the results of the FACET study did not justify the claim regarding the impact of Oxis Turbohaler 12 on the management of asthma. The Appeal Board upheld the Panel's ruling that the claim was misleading in breach of Clause 7.2.

The appeal was unsuccessful.

Complaint received **24 June 1998**

Case completed **19 November 1998**

CASE AUTH/744/7/98

GLAXO WELLCOME v ZENECA PHARMA

Accolate journal advertisement

Glaxo Wellcome complained about a journal advertisement for Accolate (zafirlukast) issued by Zeneca Pharma. A claim that " 'Accolate' is the first of a new class of oral therapy with this indication" was alleged to be incorrect as montelukast, which came from the same class - leukotriene receptor antagonists, had been available in the UK for some time. The Panel noted that the claim in question was preceded by the phrase "NEW 'for the treatment of asthma.' With the decision to challenge convention, comes progress". Montelukast (Singulair) was indicated for the treatment of asthma as add-on therapy in patients with mild to moderate persistent asthma who were inadequately controlled on inhaled corticosteroids and in whom "as needed" short acting ß-agonists provided inadequate clinical control. Singulair was also indicated in the prophylaxis of asthma in which the predominant component was exercise-induced bronchoconstriction. Accolate was indicated "for the treatment of asthma". The Panel considered that although it could have been made clearer the claim in question was not unacceptable given the difference in the products' licensed indications. The Panel ruled no breach of the Code.

In relation to the claim "An advance in confident control", Glaxo Wellcome said that the minimal clinical data that was currently available pointed to inhaled steroids being more effective and so this claim was incorrect. The Panel noted that the claim appeared at the end of a paragraph which discussed the indication, the fact that Accolate was "a new class of oral therapy" and its world-wide use. The Panel further noted that the main promotional claim in the advertisement was "A tablet alternative to inhaled steroid introduction". The Panel considered that the claim "An advance in confident control" in association with the positioning of Accolate as an alternative to the introduction of inhaled steroids gave the impression that Accolate was a significant improvement over treatment with inhaled steroids. No clinical data had been provided to support this impression. The Panel ruled that the claim was misleading in breach of the Code. Upon appeal by Zeneca, the Appeal Board noted that Accolate was licensed for the treatment of asthma and acknowledged that it was an advance in available therapies. The Appeal Board considered, however, that by linking "advance" to "confident control" some readers might assume that the claim meant that Accolate was better at controlling asthma than other therapies. There was no data to show that. The Appeal Board considered that the claim was misleading and upheld the Panel's ruling of a breach of the Code.

Glaxo Wellcome UK Limited complained about a journal advertisement for Accolate (zafirlukast) (ref 98/9556 JJJ) issued by Zeneca Pharma which had appeared in the British Medical Journal, 18 July 1998.

1 Claim " 'Accolate' is the first of a new class of oral therapy with this indication"

COMPLAINT

Glaxo Wellcome stated that as montelukast, which came from the same class (leukotriene receptor antagonists), had been available in the UK for some months, this claim was incorrect. A breach of Clause 7.2 was alleged.

RESPONSE

Zeneca stated that it should be noted that the claim began, "NEW 'for the treatment of asthma' ... 'Accolate' is the first of a new class of oral therapy with this indication.". Presumably, Glaxo Wellcome had made the mistaken assumption that Accolate and montelukast shared the same indication for use.

Zeneca stated that a simple comparison of the therapeutic indication sections of the two respective summaries of product characteristics (SPCs) showed that the indications for use were different. Montelukast (Singulair) was indicated for the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who were inadequately controlled on inhaled corticosteroids and also for exercise-induced asthma. Accolate, on the other hand, was indicated "for the treatment of asthma". It was not restricted to mild or moderate disease. Nor was it restricted to use as add-on therapy to steroids and in exercise-induced asthma. Zeneca submitted that Accolate could be used at Steps 2, 3, 4 and 5 of the British Guidelines on Asthma Management. Montelukast was for use only as add-on therapy to inhaled corticosteroids (Step 3) and for exercise-induced asthma. It was, therefore, perfectly correct to say that Accolate was the first leukotriene receptor antagonist with the indication "for the treatment of asthma". Furthermore, Zeneca noted that the main promotional claim in the advertisement was "A tablet alternative to inhaled steroid introduction". Accolate, but not montelukast, was indicated for this use.

Zeneca submitted that the claim was correct and not in breach of Clause 7.2.

PANEL RULING

The Panel examined the advertisement. The claim in question was preceded by the phrase "NEW 'for the treatment of asthma.' With the decision to challenge convention, comes progress." The Panel noted that Accolate and montelukast were both leukotriene receptor antagonists. Singulair was indicated for the treatment of asthma as add-on therapy in patients with mild to moderate persistent asthma who were inadequately controlled on inhaled corticosteroids and in whom "as needed" short acting ß-agonists provided inadequate clinical control. Singulair was also indicated in the

prophylaxis of asthma in which the predominant component was exercise-induced bronchoconstriction. Accolate had a broader indication for the treatment of asthma. The Panel considered that although it could have been made clearer the claim in question was not unacceptable given the differences in the products' licensed indications. The Panel ruled no breach of Clause 7.2 of the Code.

2 Claim "An advance in confident control"

COMPLAINT

Glaxo Wellcome stated that the minimal clinical data that was currently available consistently pointed to inhaled steroids being more effective and so this claim was incorrect. Glaxo Wellcome alleged a breach of Clause 7.2.

RESPONSE

Zeneca noted that it appeared that Glaxo Wellcome considered this to be a claim for superiority over inhaled steroids, yet the advertisement did not contain any statement comparing Accolate with steroids or, indeed, any other therapy.

Zeneca submitted that the claim relating to an advance in control embodied three elements:

a) Accolate was a leukotriene receptor antagonist which was a new class of treatment and, therefore, an advance in medicine as any other new therapeutic class would be.

b) Accolate offered physicians new options for the control of asthma and thus advanced their therapeutic armamentarium.

c) Accolate gave physicians the option of using oral therapy from as early as Step 2. Accolate was the first new oral therapy for use at Step 2 in the last 18 years.

In addition Zeneca submitted that the claim relating to confidence in control embodied a number of elements:

a) Accolate was of proven efficacy in improving parameters of asthma control when added to ß2-antagonist prn therapy alone. This demonstrated its benefits as a controller (preventer) therapy for chronic daily use. Clinicians could therefore use it with confidence in achieving therapeutic goals.

b) Experience with Accolate came not only from the clinical trial programme but also from clinical practice. Accolate entered clinical use over two years ago, was available in over twenty countries and had been taken by over one million patients in countries around the world.

c) Physicians could have confidence that patients would take Accolate. This came from the fact that it was an oral therapy not subject to the difficulties of inhaler technique. In a study on compliance 80% of patients complied with Accolate therapy (Chung *et al* 1997) and, in a European preference study, 70% of adolescent patients expressed an overall preference for Accolate in comparison with 27% of patients for inhaled steroid (beclomethasone) (data on file).

Zeneca submitted that the claim was correct and fully supportable and, consequently, not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the claim '" An advance in confident control" appeared at the end of a paragraph which discussed the indication, the fact that Accolate was "a new class of oral therapy" and its worldwide use. The Panel further noted that the main promotional claim in the advertisement was "A tablet alternative to inhaled steroid introduction".

An abstract by Chung *et al* (1997) and data on file provided by Zeneca discussed patient compliance with, and preference for, oral medication. The Panel noted that patient compliance might improve with oral medication which in turn might lead to better disease control. The Panel accepted that the introduction of an oral asthma therapy as an alternative to inhaled steroids was not insignificant.

The Panel noted that the Guidelines on Asthma Management, (1995) were agreed before the introduction in the UK of the leukotrienes. The Guidelines stated that leukotriene receptor antagonists and synthesis inhibitors..... "have been shown to have a range of potentially beneficial pharmacological properties but more studies are needed to provide comparative data against established therapies before any positioning recommendation can be made"

The Panel noted Zeneca's submission that Accolate could be used at Step 2 of the Guidelines. The current Guidelines recommended that in patients still uncontrolled on prn inhaled short acting ß2-agonists, low dose inhaled steroids should be added.

An abstract provided by Glaxo Wellcome (Laitinen *et al* (1997)) compared the efficacy of zafirlukast and low dose steroids in asthmatics on prn ß2-agonists. The authors concluded that zafirlukast produced an important level of response comparable to that of beclomethasone in the majority of patients. In some parameters beclomethasone was significantly more effective than the licensed dose of zafirlukast (20mg bd).

The Panel considered that the claim "An advance in confident control" in association with the positioning of Accolate as an alternative to the introduction of inhaled steroids gave the impression that Accolate was a significant improvement over treatment with inhaled steroids. No clinical data had been provided to support this impression. The Panel considered that the claim was misleading and a breach of Clause 7.2 of the Code was ruled.

APPEAL BY ZENECA PHARMA

Zeneca stated that it understood that the claim was considered to be in breach because it gave the impression that Accolate was "..... a significant improvement over treatment with inhaled steroids." The company noted that the Panel had considered an abstract of a study, supplied by Glaxo Wellcome, which compared the efficacy of Accolate with steroids in asthmatic patients. Based on the evidence before it, the Panel appeared to have concluded that Accolate was not more effective than steroids and, from this, formed the opinion that it was

misleading to claim that Accolate was an advance in control. No claim was actually made for Accolate being an advance in efficacy over inhaled steroids. In fact, no comparison of relative efficacies was either made or implied with any other asthma medication.

Zeneca stated that Accolate had been shown to be an effective controller therapy, adding benefits in those uncontrolled on ß2-agonist alone, and this was reflected in its licensed indication. Additional attributes other than pharmacological efficacy could make significant differences in patients' treatment eg by making administration easier or more convenient, and by improving compliance. Indeed, the Panel had noted that patient compliance might improve with oral medication which in turn might lead to better disease control. Zeneca stated that this point had also had been made by Sampson and Holgate in a recent British Medical Journal editorial.

Zeneca stated that considering the classes of agent currently recommended in the British Thoracic Society (BTS) Guidelines on Asthma Management 1995, the leukotriene receptor antagonists represented the first new class of asthma therapy to be introduced in over 20 years in the UK. There had been pharmaceutical innovations during that period, in the form of longer-acting agents and improved inhaler devices, but no new therapeutic class. Zeneca noted that the Panel accepted that the introduction of an oral asthma therapy as an alternative to inhaled steroid was not insignificant. The company found it difficult to accept that what Sampson and Holgate referred to as "....an entirely new class of asthma treatment" could not be described as an advance. The fact that these agents were also taken orally gave them an added advantage for doctors and patients over the inhaled route.

Zeneca stated that Accolate was indicated "for the treatment of asthma" in patients 12 years of age and over, permitting its use as a first-line controller therapy. This provided clinicians with a new choice when they were considering the initiation of controller treatment. This indication was also one feature which distinguished Accolate from the only other leukotriene receptor antagonist available in the UK, montelukast, which was indicated as add-in therapy to inhaled corticosteroids. Zeneca considered Accolate to be an advance in the chronic control of asthma, affording clinicians a new choice in first-line controller therapy.

Zeneca noted that the Panel considered the BTS Guidelines on Asthma Management and noted the statement contained therein on leukotriene antagonists. The company noted that these guidelines were drawn up in 1995, some three years before the introduction of leukotriene antagonists into the clinical management of asthma in the UK. The British Thoracic Society could not reasonably have recommended these agents for a given place in clinical practice in 1995 when none were available for UK doctors to prescribe until 1998. It was important, therefore, that physicians be given some direction on where Accolate might reasonably be used within its licence in their management of patients. This had to be done without implying that the British Thoracic Society had placed Accolate in the guidelines as this would certainly mislead readers. It was for this reason that the final statement on the advertisement "a tablet alternative to inhaled steroid introduction" was simply a positioning statement to give that guidance to physicians.

Zeneca stated that as could be seen from the advertisement, its positioning statement was quite distinct and physically separated from the claim of an advance in confident control. Indeed, the two statements were in distinct typeset. It was an established principle that it was not appropriate to require two separated statements to be read together in order to convey a correct meaning. Zeneca thought particularly of the use of a separate statement which qualified a broad claim elsewhere in an advertisement. Accordingly, it was inappropriate to deliberately read together two statements relating to different points about a product in order to read a particular, and incorrect, meaning into an advertisement. The company noted that the ruling on this case had centred on the impression the Panel had drawn from the advertisement. Zeneca considered this impression could only be gained by reading too much into two disparate statements. The company did not consider clinicians, reading this advertisement in isolation, would draw the same conclusion as the Panel.

In conclusion, Zeneca considered that the advertisement did not give the impression that Accolate was a significant improvement over treatment with inhaled steroids. Nowhere in the advertisement was a comparison of relative efficacies with any other asthma medication either made or implied. The impression might only be arrived at by the inappropriate and contrived reading together of two disconnected statements.

The company presented some recent market research data. During the course of a lengthy interview a number of GPs and chest physicians had been asked how they would interpret the claim "An advance in confident control". While a minority of respondents indicated that they thought the claim might be linked to the efficacy of Accolate compared with that of other therapeutic choices the company noted that such reactions were only elicited after a long and close examination of the advertisement and probing by the market researcher. The company submitted that a GP quickly reading the advertisement in a journal, would not interpret the claim in the same way.

APPEAL BOARD RULING

The Appeal Board noted that Accolate was licensed for the treatment of asthma and acknowledged that it was an advance in available therapies. The Appeal Board considered, however, that by linking "advance" to "confident control" some readers might assume that the claim meant that Accolate was better at controlling asthma than other therapies. In that regard the Appeal Board noted some of the responses which had been obtained during the market research. There was no data to show that Accolate was better than other available therapies in controlling asthma. The Appeal Board considered that the claim was misleading and upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal was unsuccessful.

Complaint received **21 July 1998**

Case completed **10 December 1998**

CASE AUTH/745/7/98

ASTRA v WYETH

Promotion of Zoton

Astra complained about the promotion of Zoton (lansoprazole) by Wyeth. Astra's product omeprazole (Losec) was referred to in some of the promotional material.

Astra alleged that misrepresentation of Baldi *et al* data occurred in a number of promotional items. The Baldi data were presented in two documents, a poster which contained the full statistical analysis, and an abstract. Astra alleged that use of the Baldi *et al* data in two documents to support the position that lansoprazole 15mg daily was equivalent to omeprazole 20mg daily in the maintenance of gastro-oesophageal reflux disease (GORD) was misleading and not based on an up to date evaluation of the evidence and a gross misinterpretation of the data.

The Panel noted that the Baldi *et al* abstract stated that there was no significant difference in outcome between lansoprazole 15mg and 30mg and omeprazole 20mg. The poster stated that endoscopic remission rate was significantly influenced by dosage. Statistically significant differences were seen in favour of lansoprazole 30mg vs 15mg and omeprazole 20mg vs lansoprazole 15mg. In patients who took at least 80% of the study medication there was no statistical difference between the products. The Panel noted that claims in a disease "Fact Book" and a lansoprazole Key Reference document had been incorrectly referenced to the Baldi abstract although they referred to results presented only in the poster. This had been acknowledged by Wyeth. Other breaches of the Code were ruled in relation to "The Fact Book" because it wrongly gave the impression that the results referred to applied to the all patient analysis and because the claim "Zoton has never been beaten in any published comparative study" was misleading because it omitted results from the Baldi study simply because it had not been published although the results had been presented in a poster at a scientific conference and were thus in the public domain. The Panel was concerned about the use of the Baldi data by Wyeth. It was very important that companies were clear and accurate about studies presented in promotional material. Wyeth had misrepresented the results. The Panel considered that this brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

Upon appeal by Wyeth of the ruling of a breach of Clause 2 of the Code, the Appeal Board considered that the selective and misleading use of data from the Baldi poster and abstract brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel's ruling was upheld.

A breach of the Code was ruled in relation to a journal advertisement because non-comparative data had been used to support the claim "Zoton 15mg - Comparable 12 month remission rates to omeprazole 20mg" and this was misleading.

A breach of the Code was also ruled in relation to a claim in the journal advertisement "Zoton 30 mg - Significantly faster symptom relief than omeprazole 20mg" which was followed by the statement "From a study of 852 patients with moderate to severe reflux oesophagitis" referenced to Castell *et al* (1996). The Panel noted that there was data to show that in reflux disease lansoprazole 30mg relieved some symptoms faster than omeprazole 20mg. With regard to other symptoms, however, there was no difference between the two medicines. The Panel considered that the claim "Significantly faster symptom relief...." would be taken by most readers to mean that all symptoms of reflux disease were relieved faster with Zoton 30mg than omeprazole 20mg which was not so. In addition, the Panel considered that the claim was misleading as to the relative clinical effectiveness of the products as there was no significant difference between the two in terms of healing rates. A breach of the Code was ruled.

Wyeth accepted the Panel's view that the claim "Significantly faster symptom relief....." would be taken by most readers to mean that all symptoms of reflux disease were relieved faster with Zoton 30mg than omeprazole 20mg which was not so. Wyeth did not, however, accept the second part of the Panel's ruling that the claim was misleading as to the relative clinical effectiveness of the products because there was no difference in healing rates. Wyeth noted that Astra did not cite this in its complaint. The Appeal Board agreed with Wyeth that the second part of the Panel's ruling with regard to the relative healing rates of the two products had been inappropriate as it had gone beyond the original allegation.

Astra Pharmaceuticals Ltd complained about the promotion of Zoton (lansoprazole) by Wyeth. Astra's product omeprazole (Losec) was referred to in some of the promotional material.

A Use of data by Baldi *et al*

COMPLAINT

Astra alleged that the misleading use of the data from Baldi *et al* (1996), which compared omeprazole 20mg with lansoprazole 15mg and 30mg once daily, constituted a breach of Clauses 7.2 and 2 of the Code.

Astra stated that Baldi *et al* was the only study which directly compared omeprazole 20mg and lansoprazole 15mg in the maintenance of gastro-oesophageal reflux disease (GORD). The study was presented as a poster at the American Gastroenterology Association (AGA) Congress 1996 and was referenced as an abstract published in Gastroenterology 1996. Astra submitted that the results from the study had been misrepresented in Zoton promotional materials, as the abstract did not contain the full balance of evidence from this study. The abstract stated that the analysis consisted of all patients treated and that there was no significant difference in outcome between the three treatment groups; a p value was not stated. The poster from this study, presented at the AGA Congress 1996, contained the full statistical analysis and showed that the primary end point of the study was endoscopic remission rates after 12 months'

maintenance treatment with an all-patients treated analysis. However, in the poster, the all-patients treated analysis of the primary endpoint showed significant differences in endoscopic remission rates between omeprazole 20mg and lansoprazole 15mg ($p<0.01$[in favour of omeprazole 20mg]) with the statement that endoscopic remission rate was significantly influenced by dosage. In a sub-group analysis of patients with compliance ≥80% no significant difference was shown between the 3 treatment groups.

Astra stated that in view of the full analysis presented in the poster, it considered that the use of the Baldi *et al* data to support the position that lansoprazole 15mg daily was equivalent to omeprazole 20mg daily in GORD maintenance was misleading, not based on an up-to-date evaluation of evidence and was a gross misrepresentation of the data and therefore constituted a breach of Clauses 7.2 and 2 of the Code. Astra was concerned that the full analysis of the data had been known to Wyeth through the Takeda European R & D Centre since 1996 and that there had been non-disclosure in the Zoton promotional materials aimed at clinicians and health authorities.

Astra stated that the misrepresentation of the Baldi *et al* data occurred in the following items:

1 Zoton Journal Advertisement (ZZOT 861A/0498)

The photocopy of the journal advertisement supplied by Astra bore the reference (ZZOT861A/0498). The advertisement supplied by Wyeth bore the reference (ZZOT858/0498). The claims at issue appeared to be the same on both advertisements.

This was dealt with as point B below.

2 Gastro-oesophageal reflux disease - The Fact Book

The photocopy of The Fact Book supplied by Astra with the complaint had the reference (ZZOT 736/1297). The Fact Book supplied by Wyeth bore the reference (ZZOT736/0298). The sections of the Fact Book at issue appeared to be identical.

Astra drew attention to two sections:

(i) "In a comparison of Zoton 15mg and 30mg and omeprazole 20mg, the proportion of patients in whom compliance was >80% who were maintained in endoscopic remission was slightly greater than in the previous study, with 91% (15mg) and 96% (30mg) of patients in the Zoton groups successfully maintained over 12 months of treatment compared with 94% of patients treated with omeprazole. There was no significant difference between the treatments in the proportion of patients who remained in endoscopic remission".

The reference cited for this section was the Baldi *et al* abstract. However, the remission rates quoted only appeared in the AGA 1996 poster and not the abstract. The conclusion that there was no significant difference between the treatments was grossly misleading, as the poster showed that the endoscopic remission rate was significantly influenced by dosage and that omeprazole 20mg was significantly more effective than lansoprazole 15mg in the all-patients analysis.

Astra stated that it had asked Wyeth to explain how the data from the Baldi *et al* poster came to be represented in this item produced in December 1997, four months before the Zoton advertisement ZZOT 861A/0498. The company had asked Wyeth to provide it with the supporting evidence for this section of the booklet, as clearly the Baldi *et al* abstract did not support the remission rates quoted. To date, Astra had not received a response to these specific requests.

(ii) "Zoton has never been beaten in any published comparative study++. (++In no published comparative study has a PPI demonstrated a statistically significant advantage over Zoton at recommended doses in licensed indications for Zoton)."

This statement appeared on the back page of the booklet. The specific use of "published comparative study" in this context was particularly unacceptable, as the full results of the Baldi *et al* study had been known to Wyeth since 1996, but had not been published as a paper. Furthermore, the Baldi *et al* study involved 906 patients which represented a sizeable set of data in reflux oesophagitis maintenance. Astra stated that in this context, the use of the statement "Zoton has never been beaten in any published comparative study" was economical with the truth.

3 Lansoprazole Key References - Summary of Key Clinical References - Hospital (ZZOT740/0797)

Astra stated that since first writing to Wyeth with this complaint, the above item had come to its attention. This item was produced in July 1997 and contained a one page summary of the Baldi *et al* study. The summary presented the results from two groups of patients: all patients treated and patients with compliance ≥80%. No p values were stated; the Baldi *et al* abstract and Data on file Wyeth (105806) were cited as references. The results for the all patients treated group were identical to those presented in the AGA 1996 poster, however the conclusion stated:

> "The authors concluded that lansoprazole 15mg and lansoprazole 30mg is as safe and effective as omeprazole 20mg in the maintenance treatment of reflux oesophagitis."

Astra stated that this item was further evidence that there had been selective and misleading use of data when the full analysis of the Baldi *et al* study was available to Wyeth. Astra stated that it would be interested to know what data were available in Data on file Wyeth (105806).

Astra stated that in addition to its concerns about the misrepresentation of the Baldi *et al* data in Zoton promotional items, it was particularly concerned to see how these data were presented in response to Case AUTH/676/2/98 in which Wyeth stated that:

> "The only direct head to head comparison of 15mg Zoton vs 20mg omeprazole in the maintenance of reflux oesophagitis is Baldi. Endoscopic remission rates at 12 months showed no statistically significant difference between lansoprazole 15mg and omeprazole 20mg".

In summary, Astra alleged that there had been gross misrepresentation of the Baldi *et al* data by selective use of

subset data and omission of primary all-patients treated data. The Baldi *et al* study had been used as a supporting reference for key claims in the Zoton campaign with non-disclosure of the full analysis of the data. Astra alleged breaches of Clauses 7.2 and 2 of the Code.

Astra stated that it was aware that the claims referred to above were in use, not only in the items ZZOT861A/0498, ZZOT736/1297 and ZZOT740/0797 but also in a number of other materials. A list was provided.

RESPONSE

Wyeth stated that before dealing with Astra's complaint regarding some of its promotional material the company would like to clarify the situation regarding the data by Baldi *et al*.

Wyeth stated that the complete report on this study had not been available to it through the Takeda European R & D Centre since 1996, indeed the company was not in receipt of the final report relating to this study at the time of replying to Astra's informal approach on 8 July 1998. Wyeth refuted any accusation that it had been withholding data.

Wyeth acknowledged that it had referenced both the Baldi abstract (Baldi F *et al*. Gastroenterol 1996; 110 (4): Suppl A55 (107136)) and poster (Data on file, Wyeth (105806)).

This was a conscious decision. Pending receipt of the definitive report, the company considered that it was appropriate to use both the abstract and the poster in the appropriately qualified context, so ensuring that all the data it had available at any one time was disclosed.

In using the abstract, the company had specified the data on the stated "all patients treated" analysis. Though it was stated that "there was no significant difference between the treatments", Wyeth was unable to state the p value as none was given in the abstract.

In using the poster data, the company had presented both the "all patients treated" data as well as "patients treated with compliance ≥80%". Wyeth considered that the use of the ≥80% compliance efficacy data was a closer representation of the true efficacy of the specified medications, particularly as there were no significant differences between the three treatments when considering the intention to treat safety (tolerance) analysis. Wyeth stated that it had made it perfectly clear that it was referring to patients with a compliance of ≥80% and that given this context that its conclusions were therefore valid and neither misleading nor misrepresentative.

Wyeth turned to the specific promotional items referred to by Astra.

1 Zoton Journal Advertisement

This was dealt with under point B below.

2 Gastro-oesophageal reflux disease - The Fact Book, ZZOT736/1297

(i) Referencing of the Baldi *et al* data

Wyeth thanked Astra for bringing to its attention the referencing in the Fact Book. It had been mistakenly printed as referring to the Baldi *et al* published abstract, rather than as data on file (ie referring to the poster). However in this book it was clearly stated that the company was referring to patients whose compliance was ≥80%, the data was therefore not misleading.

(ii) "Zoton has never been beaten in any published comparative study"

Wyeth submitted that this was factually correct, as the company had told Astra in its letter of July 1998 that it had been informed that it would soon be in receipt of a copy of the final report relating to the study. As stated previously, Astra's assertion that full results had been known to Wyeth since 1996 was factually incorrect.

3 Lansoprazole Key References - Summary of Key Clinical References - Hospital (ZZOT740/0797)

Wyeth referred to the claim at issue, "The authors concluded that lansoprazole 15mg and lansoprazole 30mg is as safe and effective as omeprazole 20mg in the maintenance treatment of reflux oesophagitis" and stated that the results text clearly stated that there was no significant difference in patients where compliance was ≥80%. The conclusion was perfectly satisfactory in that it was obviously associated with the ≥80% compliance context. The company acknowledged that p values were not stated on the "all patients treated" paragraph. The data on file referred to was the Baldi *et al* poster.

Wyeth stated that this item had not been available for some time.

PANEL RULING

The Panel decided to deal with the allegation concerning the journal advertisement under point B below as there were other allegations about it.

The Panel noted that the Baldi *et al* abstract stated that there was no significant difference in outcome between lansoprazole 15mg and 30mg and omeprazole 20mg. All treatments were well tolerated. The abstract concluded that "In this the largest comparative study, lansoprazole 15mg and 30mg is as effective and safe for the treatment of reflux oesophagitis and gives results comparable with omeprazole 20mg". The Baldi *et al* poster gave more details about the study and stated that endoscopic remission rate was significantly influenced by dosage. Endoscopic remission at 12 months gave the results in all patients as 76% for lansoprazole 15mg, 91% for lansoprazole 30mg and 90% for omeprazole 20mg. Statistically significant differences were seen in favour of lansoprazole 30mg vs 15mg and omeprazole 20mg vs lansoprazole 15mg. The poster stated that in patients who took at least 80% of the study medication there was no statistical difference between the products. The endoscopic remission at 12 months in these patients were given as 91% for lansoprazole 15mg, 96% for lansoprazole 30mg and 94% for omeprazole 20mg.

With regard to the Fact Book, the Panel noted that it had been incorrectly referenced to the Baldi abstract. The Fact Book referred to the results presented only in the poster. The Fact Book should have been referenced to the poster.

This had been acknowledged by Wyeth. The Panel considered that it was misleading to refer only to the results in patients who took at least 80% of the study medication. The primary analysis was all patients and these results should have been given particularly as they showed a statistically significant difference between omeprazole 20mg and lansoprazole 15mg. The impression from the Fact Book was that the results applied to the all patient analysis and this was not so. The Panel considered that the Fact Book was misleading and ruled a breach of Clause 7.2 of the Code.

The Panel considered that the claim in the Fact Book "Zoton has never been beaten in any published comparative study" was misleading. It was disingenuous to omit results from a study simply because that study had not been published particularly as it was the only direct head to head comparison of Zoton and omeprazole in the maintenance of GORD. The results had been presented in poster form at a scientific conference and were thus in the public domain. A breach of Clause 7.2 of the Code was ruled.

With regard to the Lansoprazole Key References document, the Panel noted that the page giving details of the Baldi data was referenced to the abstract although the data given was only presented in the poster. The Panel considered that its ruling regarding the Fact Book also applied to the Key References document. A breach of Clause 7.2 was ruled.

The Panel was very concerned about the use of the Baldi *et al* data by Wyeth. It was very important that companies were clear and accurate about studies presented in promotional material. Wyeth had misrepresented the results of the Baldi study. The Panel considered that the misleading use of the data brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Following the Panel's consideration of this allegation the Panel noted that the Lansoprazole Key References document referred to lansoprazole as being "as safe and effective...". The Panel considered that this was not in accordance with Clause 7.7 of the Code which prohibited the use of the word "safe" without qualification. The Panel requested that this be drawn to Wyeth's attention.

APPEAL BY WYETH

Wyeth appreciated that the application of Clause 2 was a matter of judgement for the Panel and the Appeal Board. The company accepted that its presentation of the Baldi data fell short of the standards required of it as a responsible company but it appealed the Panel's ruling of a breach of Clause 2 for the following reasons:

1 The complaint arose in the context of a keen and ongoing rivalry between Wyeth and Astra.

2 The company had reviewed all published Code of Practice cases since August 1995 where breaches had been ruled and found that, out of a total of 193 cases, 87 (45%) included a Clause 7.2 ruling but none resulted in a ruling under Clause 2.

3 In addition, in a recent ruling on a complaint by Wyeth against Astra (Case AUTH/677/2/98) in respect of Losec, Astra were judged to have committed 9 breaches of Clause 7.2 and one each of Clause 7.6 and 81. However, no Clause 2 breach was ruled (a summary detailing the reasons for each ruling of a breach of the Code was provided).

4 Wyeth noted that in this particular case Astra complained specifically under Clause 2 whereas Wyeth in its complaint against Astra did not. Wyeth requested the Appeal Board to consider whether this had resulted, albeit inadvertently, in a lack of consistency in the Panel's rulings.

Wyeth stated that it regarded a finding under Clause 2 as a very serious matter which had internal as well as external implications for the company. Since this complaint occurred, the company's internal compliance procedures had been reviewed and modifications made. Nevertheless, Wyeth recognised the importance of effective self-regulation within the industry and invited the Authority to audit its internal procedures if it considered that this would be appropriate.

APPEAL BOARD RULING

The Appeal Board noted the Panel's ruling of a breach of Clause 7.2 of the Code in relation to the use of the Baldi data in promotional material. Wyeth had accepted the ruling of a breach of Clause 7.2 and regarded the ruling of a breach of Clause 2 to be a very serious matter.

The Appeal Board considered that Wyeth had selectively quoted those results from the Baldi poster and abstract which demonstrated equivalence of Zoton 15mg and omeprazole 20mg. The primary endpoint of the study had been endoscopic remission rates after 12 months' maintenance treatment with an all patients treated analysis. The poster detailed this result and showed a statistically significant advantage in favour of omeprazole 20mg.

The Appeal Board was concerned that Wyeth had not seen the final report on the Baldi study. Companies must be certain that the data presented in promotional material was accurate and balanced. The Appeal Board considered that the selective and misleading use of data from the Baldi poster and abstract brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2 of the Code.

The appeal on this point was unsuccessful.

B Zoton Journal Advertisement

1 Claim "Zoton 15mg - Comparable 12 month remission rates to omeprazole 20mg"

The claim was followed by the statement "Endoscopic remission rate ranges: Zoton 15mg 69-87% and omeprazole 20mg 74-89%".

The endoscopic remission ranges for Zoton were referenced to five studies one of which was the Baldi *et al* abstract and the endoscopic remission ranges for omeprazole were referenced to three other studies one of which was also the Baldi *et al* abstract.

COMPLAINT

Astra alleged that the first part of the claim, "Zoton 15mg - Comparable 12 month remission rates to omeprazole 20mg" was a misrepresentation of the Baldi *et al* data in breach of Clause 7.2 and 2 of the Code.

In addition to its concerns regarding the Baldi *et al* data Astra noted that the claim was also supported by comparing the results of two groups of non-comparative studies, implying similar ranges in terms of percentage of patients in endoscopic remission at 12 months. Astra stated that these data were not comparable. None of the studies were designed (unlike the Baldi study) to directly compare lansoprazole 15mg and omeprazole 20mg. As such, they could not answer the question of relative efficacy. The studies were not randomized controlled comparisons of Zoton 15mg and omeprazole 20mg and, as such, were subject to a large number of biases. In addition the studies quoted had different entry criteria based on different grades of oesophagitis at entry and different oesophagitis grading systems. The patients involved in the studies were therefore different in terms of disease. The studies quoted had different criteria for endoscopic remission based on different oesophagitis grading systems. The end point remission rates were, therefore, non-comparable as they involved different levels of healing of oesophagitis measured on different criteria.

Astra stated that the only scientifically valid comparison had shown lansoprazole 15mg to be significantly less effective than omeprazole 20mg in GORD maintenance over one year in a large trial of 906 patients (Baldi *et al*). This supported the conclusion that omeprazole 20mg was significantly more effective than lansoprazole 15mg in GORD maintenance.

Astra alleged that use of non-comparable, non-comparative studies in this unscientific fashion was misleading and in breach of Clause 7.2 of the Code.

RESPONSE

Wyeth acknowledged that the claim "Zoton 15mg - Comparative 12 month remission rates to omeprazole 20mg" was inappropriate and did not accurately reflect the data presented by Baldi *et al*. Wyeth stated that it was currently reviewing all of its materials to ensure that the claim had been amended appropriately.

Wyeth made no comment regarding the second part of Astra's complaint.

PANEL RULING

The Panel considered that its rulings of breaches of Clauses 7.2 and 2 of the Code concerning the use of the Baldi *et al* data made in point A above would also apply here.

The Panel considered that the use of non comparative data to support the claim "Comparable 12 month remission rates to omeprazole 20mg" was misleading and a breach of Clause 7.2 of the Code was ruled.

APPEAL BY WYETH

Wyeth appealed the Panel's ruling of a breach of Clause 2 (see point A above)

APPEAL BOARD RULING

The Appeal Board's ruling of a breach of Clause 2 made in point A above also applied here.

2 Claim "Zoton 30mg - Significantly faster symptom relief than omeprazole 20mg"

The claim was followed by a statement "From a study of 852 patients with moderate to severe reflux oesophagitis" referenced to Castell *et al* (1996).

COMPLAINT

Astra stated that the claim did not reflect an up-to-date evaluation of the balance of evidence. A review of the data examining symptom relief in GORD revealed that in three of the studies which examined symptom relief, clear differences were not apparent between the medicines (Corallo *et al* (1993), Vcev *et al* (1997) and Petite *et al* (1995)). Of the three studies where differences in symptom relief were apparent, the data suffered from internal contradictions in one study (Hatlebakk (1993)) where symptom relief rates as recorded by patients were not reflected in clinical records. In the final two studies (Mee and Rowley (1996) and Castell *et al* (1996)) (one of which, Castell *et al*, was cited as a reference for the statement) multiple significance testing would influence the calculation and interpretation of statistical significance.

Astra alleged that on this basis, to state "Zoton 30mg - Significantly faster symptom relief than omeprazole 20mg" was misleading, unbalanced and not adequately qualified by the statement immediately below. This claim was therefore in breach of Clause 7.2 of the Code.

RESPONSE

Wyeth stated that the claim was clearly discussing a single study in which Zoton 30mg had significantly faster symptom relief than omeprazole 20mg in patients with severe to moderate reflux oesphagitis. The study, by Castell *et al*, involved over 800 patients and significantly faster symptom relief was seen with lansoprazole 30mg at both day 1 and day 7 ($p<0.05$). The claim was not a general one regarding symptom relief between Zoton 30mg and omeprazole 20mg.

Wyeth stated that a total of 7 comparative studies had been conducted, three of these studies clearly showed a significant benefit in Zoton's favour (Hatlebakk *et al* (1993), Mee and Rowley (1996), Castell *et al* (1996)), one showed a trend (Petite data on file), two showed no difference (Carollo *et al* (1993), Vcev *et al* (1997)) and one did not report on symptom relief (Rampal (1995)).

Wyeth stated that a publication of a meta analysis by Huang and Hunt at the recent American Gastroenterology Association meeting also added further weight to this argument. The authors were accepted experts on this type of analysis, and the entry criteria were very specific. The overall conclusion of the study was "Lansoprazole relieved significantly more symptoms than omeprazole at the first 2 weeks of treatment".

PANEL RULING

The Panel noted that a similar allegation had been considered in previous cases involving Zoton (Cases AUTH/165/6/94 and AUTH/166/6/94). In these cases a claim "Faster symptom relief than ... omeprazole ..." had been ruled to be misleading as although at that time there had been some evidence to support the claim it was insufficient to support an unqualified claim for faster relief. The claim was misleading as to the relative clinical effectiveness of the products as there was no difference between the two products in terms of the final outcome. The Panel's ruling had been upheld on appeal.

The Panel noted Wyeth's submission that there were seven studies comparing lansoprazole 30mg with omeprazole 20mg daily in the treatment of reflux oesophagitis. With regard to onset of symptom relief three studies showed a benefit in Zoton's (lansoprazole's) favour, one showed a trend in favour of Zoton, two showed no significant difference between the two medicines and one did not report on symptom relief.

Mee *et al* (1996) assessed daytime heartburn/epigastric pain, night-time heartburn/epigastric pain and dysphagia/odynophagia. According to the patients' own assessments, after 3 days of treatment there was a significant improvement in symptoms of daytime heartburn in the lansoprazole group compared to the omeprazole group (p=0.05). There was no significant difference observed between the two treatments for epigastric pain or night-time heartburn. According to clinical assessment a significantly greater improvement in daytime epigastric pain was observed in the lansoprazole group compared with omeprazole after 1 and 8 weeks of treatment (p=0.03 and p=0.05 respectively). A similar trend was observed in night time epigastric pain. There was no significant difference observed between the two treatment groups at any time point with respect to any of the other symptoms assessed. There was no significant difference in healing rates between the two treatment groups.

Hatlebakk *et al* (1993) assessed heartburn, acid regurgitation and dysphagia. After 4 weeks' treatment patients receiving lansoprazole 30mg had experienced a greater improvement in heartburn than patients receiving omeprazole 20mg (p=0.03). After 8 weeks the difference was no longer statistically significant. For dysphagia or regurgitation no statistically significant difference in effect was apparent at any time. There was no significant difference in healing between the two treatment groups.

Castell *et al* (1996) examined the effects of lansoprazole 30mg, lansoprazole 15mg and omeprazole 20mg and assessed day heartburn, night heartburn, belching, gastroesophagal regurgitation and painful swallowing, as well as an evaluation of overall symptoms. This study was cited in support of the claim in question. With regard to lansoprazole 30mg and omeprazole 20mg the authors reported that according to patients those receiving lansoprazole experienced significantly less day and night heartburn than did those receiving omeprazole. The clinicians however, reported no statistically significant differences between lansoprazole 30mg and omeprazole 20mg. With regard to healing rates, they were comparable in both groups.

The Panel noted, therefore, that there was data to show that in reflux disease lansoprazole 30mg relieved some symptoms faster than omeprazole 20mg. With regard to other symptoms, however, there was no difference between the two medicines. The Panel considered that the claim "Significantly faster symptom relief..." would be taken by most readers to mean that all symptoms of reflux disease were relieved faster with Zoton 30mg than omeprazole 20mg which was not so.

In addition the Panel considered that the claim was misleading as to the relative clinical effectiveness of the products as there was no significant difference between the two in terms of healing rates. A breach of Clause 7.2 was ruled.

APPEAL BY WYETH

Wyeth accepted the Panel's view that the claim "Significantly faster symptom relief ..." would be taken by most readers to mean that all symptoms of reflux disease were relieved faster with Zoton 30mg than omeprazole 20mg which was not so.

Wyeth did not, however, accept the second part of the Panel's ruling that the claim was misleading as to the relative clinical effectiveness of the products because there was no difference in healing rates. Wyeth noted that Astra did not cite this in its complaint.

Wyeth maintained that there was a clear distinction to be drawn between the speed of onset of symptom relief and healing rates. The former related to the onset of healing, which was usually manifest as the start of an improvement in symptom relief, whilst the latter referred to completed healing and was usually verified endoscopically. Given this distinction, the company considered that its claim clearly only related to the onset of healing and was not in any way giving the impression of a superior healing rate. Indeed, the company was fully aware that the healing rates were similar for the products.

APPEAL BOARD RULING

The Appeal Board noted that Wyeth had accepted the Panel's view that the claim was misleading in breach of Clause 7.2 of the Code as only some, not all, symptoms were relieved faster with Zoton 30mg than omeprazole 20mg. The Appeal Board agreed with Wyeth that the second part of the Panel's ruling with regard to the relative healing rates of the two products had been inappropriate with respect to the claim in question as it had gone beyond the original allegation.

The appeal on that point was successful.

Complaint received **20 July 1998**

Case completed **18 November 1998**

CASE AUTH/748/7/98

THE LIPOSOME COMPANY v NEXSTAR

Promotion of AmBisome and DaunoXome

The Medicines Control Agency referred to the Authority a complaint which it had received from The Liposome Company about the promotion of AmBisome (liposomal amphotericin B) and DaunoXome (liposomal daunorubicin) by NeXstar.

Firstly, The Liposome Company complained about a letter inviting recipients to a symposium to be held at a forthcoming conference. The letter, on NeXstar company headed notepaper, gave a brief overview of the scientific papers to be presented at the symposium and in doing so The Liposome Company considered that it promoted unlicensed indications for AmBisome and DaunoXome. The letter was signed by a professor of haematology. The Liposome Company alleged that the invitation constituted disguised promotion for AmBisome and DaunoXome. In addition, the company pointed out that the symposium itself referred to unlicensed uses of medicines.

The Panel noted that the Code did not prohibit the legitimate exchange of medical and scientific information during the development of a medicine provided that such activity did not constitute promotion. The Panel considered that sponsored symposia at major scientific meetings were a legitimate activity for a pharmaceutical company to undertake provided that the arrangements were in accordance with the Code. The Panel considered that the symposium which, in the conference material, was clearly linked to NeXstar, appeared to be scientific and non-promotional and no breach of the Code was ruled in that regard.

The Panel noted that the invitation to the NeXstar symposium was on company headed notepaper and, although it was signed by an independent professor of haematology, under the Code NeXstar was responsible for the letter. Although the licence for AmBisome had recently changed, at the time the letter of invitation was issued it referred to an unlicensed use of the product. The Panel considered that the positive way in which this indication was referred to promoted such a use. Similarly the Panel considered that the letter promoted DaunoXome for an unlicensed indication. Breaches of the Code were ruled. Overall the Panel considered that the letter of invitation was disguised promotion for AmBisome and DaunoXome in breach of the Code.

The Liposome Company also complained about a copy of an abstract which had been distributed by NeXstar representatives. Handwritten at the bottom of the abstract were comparative costs of AmBisome and Abelcet (The Liposome Company's product) which showed an advantage for AmBisome. The Liposome Company alleged that the cost comparison was unfair, inaccurate and intended to mislead.

In the Panel's view the abstract had been used to promote AmBisome. The handwritten data had been taken from incorrect information which had been presented at a conference. Nevertheless pharmaceutical companies were responsible for the accuracy of promotional material. The price information was misleading and a breach of the Code was ruled.

In accordance with Regulation 5 of the Medicines (Monitoring of Advertising) Regulations 1994, the Medicines Control Agency (MCA) referred a complaint it had received from The Liposome Company Ltd regarding the promotion of AmBisome (liposomal amphotericin B) and DaunoXome (liposomal daunorubicin) by NeXstar Pharmaceuticals Ltd. The complainant agreed to the matter being referred to the Authority. The MCA considered that as the complaint referred, firstly, to a one-off event (an invitation to a conference symposium) and, secondly, to the activities of a representative it would be more suitably handled by the Authority.

1 Letter of invitation to attend sponsored symposium

The letter invited recipients to a symposium to be held at the British Society of Haematology (BSH) Meeting in April 1998. The letter was printed on NeXstar headed paper and had been signed by a professor of haematology who was to act as the symposium chairman. The letter gave a brief overview of the papers to be presented at the symposium.

COMPLAINT

The Liposome Company noted that the letter advertised a presentation entitled "Review of empirical antifungal therapy in febrile neutropenia". As the letter implied, this presentation would focus on the data obtained from a large randomised, double-blind study which would show an advantage of liposomal amphotericin B (AmBisome) over conventional amphotericin B for antibiotic resistant febrile neutropenia.

The Liposome Company noted that AmBisome was not indicated for empiric treatment. The two indications for AmBisome were the treatment of severe systemic and/or deep mycoses where toxicity (particularly nephrotoxicity) precluded the use of conventional systemic amphotericin B in effective dosages, and the treatment of visceral leishmaniasis in immunocompetent patients including both adults and children.

The Liposome Company alleged that this promotional material was disguised as an invitation from the professor of haematology, to a scientific meeting, but it was distributed by NeXstar on company headed paper. Furthermore, this invitation was not inviting the recipient to the actual BSH scientific conference but instead to a symposium which was totally funded by, and where all presentations were given on behalf of, NeXstar. The Liposome Company alleged that the letter was a promotional item as it made several claims such as "an advantage of .....(AmBisome) over the conventional drug" and "....another study breaking new ground.....showing a benefit of AmBisome". In the company's opinion these

were clearly intended to advertise AmBisome.

The Liposome Company noted that the fourth paragraph referred to DaunoXome which had shown "....great promise....". Again, this could be construed as promotion, which raised concern when later in the same paragraph NeXstar referred to "....high and low grade lymphoma patients". DaunoXome was indicated for the treatment of Karposi's Sarcoma, not lymphoma.

The Liposome Company considered that both the letter and the NeXstar sponsored symposium where these papers were presented must be considered as promotional activities for AmBisome and since neither complied with the approved product information, each was in breach of the advertising regulations.

The Liposome Company considered that these were serious offences and therefore needed to be addressed to prevent them occurring again in the future. As the letter had already been mailed and the symposium had also already taken place the company considered that it might be appropriate for, at least, a letter of apology to be forwarded to all medical professionals included on the original mailing list.

The Authority noted that the complaint would be judged in relation to the Code. NeXstar's attention was drawn to the requirements of Clauses 3.2 and 10.1 of the Code.

RESPONSE

NeXstar stated that it was unable to accept the allegations. The allegation that the symposium to which the invitation referred was a promotional meeting on behalf of NeXstar Pharmaceuticals and not part of the actual BSH Scientific Conference, was untrue.

NeXstar stated that the symposium which it sponsored was a formal part of the 38th British Society of Haematology Annual Scientific Meeting and was approved by the Scientific Secretary of the Society as an educational meeting and appeared in the programme. The speakers were all practising clinicians with no affiliation to NeXstar, speaking about their research and there was no input from any company representative into the details of the presentation. The professor who had signed the letter of invitation had written to NeXstar and confirmed this to be so. NeXstar noted that the Code made it clear in Clause 1.2 that "the term 'promotion' means any activity undertaken by a pharmaceutical company or with its authority which promotes the prescription, supply, sale or administration of its medicines". NeXstar submitted that the symposium was not undertaken by the company or with its authority. NeXstar had provided sponsorship for the symposium which was undertaken by independent experts with the authority of the British Society of Haematology (BSH). Had the BSH not given its authority then the symposium would not have taken place. It was essential to distinguish this type of meeting from a true company meeting, which would take place at the time and in a location, and with material, determined by the company, and would, without doubt, be promotional and need to comply with Clause 3.2 of the Code. The professor of haematology made it clear in his letter to the company that the role of formal symposia at scientific congresses such as BSH was to inform senior clinicians of new developments and that the presentation of data relating to unauthorised products or indications was an important feature. NeXstar provided a letter written on behalf of the BSH confirming this point. This letter cited as an example of educational content the symposium sponsored by The Liposome Company at the 1995 BSH Annual Scientific Meeting. NeXstar added that in the symposium sponsored by The Liposome Company at BSH the following year a presentation referred to the use of its product, Abelcet (amphotericin B lipid complex), in the treatment of presumed fungal infections, which was and remained outside the terms of its marketing authorization. It was therefore untenable for The Liposome Company to claim that the meeting sponsored by NeXstar was a promotional meeting.

NeXstar pointed out that if it was accepted that the symposium was not promotional within the meaning of Clause 1.2 of the Code, then it must also be accepted that the letter prepared by the chairman was non-promotional. The chairman, as an independent expert, was free to write as he saw fit about medicines. That the letter appeared on NeXstar's company headed paper was immaterial. This was done in order to comply with Clause 19.3 of the Code requiring that company sponsorship of meetings be declared. In retrospect, NeXstar could also see how this had enabled The Liposome Company to lodge a complaint and therefore in future the company would request that chairpersons use their own headed paper with a clear declaration of NeXstar's sponsorship included in the text. This did not affect NeXstar's opinion that the letter was not promotional.

NeXstar also refuted the allegation that the letter was disguised promotion. The supplementary information to Clause 10.1 of the Code indicated clearly what was meant by disguised promotion and the professor's letter did not fall under those descriptions.

In conclusion, NeXstar maintained that the meeting in question was not promotional and that the letter of invitation came from an independent expert with no affiliation to NeXstar and represented his views on what was being presented at the symposium.

NeXstar pointed out that the marketing authorization for AmBisome had been extended to include empirical antifungal therapy in febrile neutropenic patients. Current and previous summaries of product characteristics (SPCs) were provided for AmBisome as well as the SPC for DaunoXome.

PANEL RULING

The Panel noted that Clause 3 of the Code stated that a medicine must not be promoted prior to the grant of its marketing authorization which permitted its sale or supply. The supplementary information to Clause 3 stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion which was prohibited under Clause 3 or any other clause. The Panel recognised the importance of the exchange of information about medicines.

The Panel considered that sponsored symposia at major scientific meetings were a legitimate activity for a

pharmaceutical company to undertake provided that the arrangements were in accordance with the Code.

The Panel noted that in the conference programme and the notes that accompanied the symposium, the symposium was clearly linked to NeXstar. The Panel noted that the letter of invitation to the NeXstar symposium was headed with the company name in logo type and its address. The letter had been signed by the professor of haematology. The Panel noted that no affiliation had been given for the professor. It was impossible to tell from the letter whether he was writing independently or as an employee of NeXstar. Under the Code NeXstar was responsible for the letter. The Panel noted that the letter was addressed "Dear Colleague". It did not know who had been invited to the symposium.

The Panel noted that the letter of invitation give a brief overview of the four papers to be presented at the symposium. One paper "Review of empirical antifungal therapy in febrile neutropenia" was described in more detail than the others. It was stated that data would be presented which showed "an advantage of liposomal amphotericin B (AmBisome) over the conventional drug in the prevention of breakthrough fungal infection in patients treated empirically for antibiotic resistant febrile neutropenia". In the Panel's view, this positive claim for the empirical use of AmBisome was promotional. The Panel noted that at the time of the symposium (April 1998) AmBisome was not licensed for the empirical treatment of febrile neutropenia (ref SPC dated 7 February, 1996) although this indication was added later (SPC dated 21 July, 1998). The Panel considered that the letter promoted the use of AmBisome for an unlicensed indication. A breach of Clause 3.2 was ruled in that regard.

The Panel noted that the letter of invitation, in referring to another paper to be presented at the symposium, stated that "liposomal daunorubicin (DaunoXome) had shown great promise in both high and low grade lymphoma patients who had failed on conventional therapy". In the Panel's view this was a promotional claim for the use of DaunoXome in high and low grade lymphoma patients. The Panel noted that DaunoXome was not licensed for use in such patients (ref SPC dated 14 February 1997). The Panel considered that the letter promoted the use of DaunoXome for an unlicensed indication. A breach of Clause 3.2 was ruled in that regard.

Overall the Panel considered that the letter of invitation was disguised promotion for AmBisome and DaunoXome and ruled a breach of Clause 10.1 of the Code.

The Panel noted that, once at the meeting, it would be acceptable for doctors to be given details about studies investigating unlicensed uses of AmBisome providing that such information was non-promotional, scientific in nature and accurate.

The Panel noted that the symposium programme included another letter from the professor together with abstracts of the presentations. The Panel had no evidence about what happened at the symposia. The Panel considered however that it appeared to be scientific and non promotional. No breach of the Code was ruled in that regard.

The Panel noted NeXstar's view that independent experts were free to write as they liked about medicines. The problems arose when pharmaceutical companies were involved in producing and/or distributing such letters.

2 Copy of an abstract

The abstract was printed on a single A4 sheet and appeared to have been presented at the 1997 meeting of the American Society of Haematology (ASH). The abstract gave brief details of a study comparing AmBisome and The Liposome Company's product, Abelcet, in the management of haematological malignancies. Handwritten at the bottom of the abstract were details of the costs of AmBisome and Abelcet. AmBisome appeared to be less expensive than Abelcet.

COMPLAINT

The Liposome Company stated that the abstract had been presented at a number of international conferences: American Society of Haematology, European Bone Marrow Transplantation, British Society of Haematology and European Confederation of Medical Mycology. The abstract itself was above reproach, but the company's concern centred around the handwritten costing included on the bottom of the abstract. The abstract was being distributed across the UK by NeXstar representatives. The copy provided to the Authority was supplied to a medical professional. When the representative was asked to justify the costing she was unable to do so. This was not surprising since the cost for Abelcet was incorrect and would mislead medical professionals. The actual NHS list price for Abelcet was £0.86 per mg, but if the figures were taken from the abstract Abelcet cost £1.60 per mg, almost double. This was inaccurate, unfair and intended to mislead. The Liposome Company alleged that representatives who were distributing this information were breaching the Medicines Act. The company also considered that the inaccuracies should be brought to the attention of the medical professionals who had received this information.

The Authority noted that the complaint would be judged in relation to the Code. NeXstar's attention was drawn to Clauses 4.1 and 7.2 of the Code.

RESPONSE

NeXstar stated that the abstract contained data which related to a licensed indication of AmBisome (the treatment of severe systemic and/or deep mycosis where toxicity precluded the use of conventional amphotericin B). The photocopy provided by The Liposome Company contained a handwritten amendment made by a hospital representative, quoting costing data presented by the authors at the American Society of Haematology Annual Meeting in 1997. NeXstar provided a letter from the principal author confirming that the data had been incorrectly presented. NeXstar did not consider that blame should be attached to the hospital representative in question who had no intention of misleading the professional to whom she gave the abstract. The representative had stated that she was not asked to justify the costing, in contradiction of the claim made by The Liposome Company's letter of complaint. NeXstar stated that it was happy to write to the medical professional

concerned to point out that the data presented at ASH contained an error.

NeXstar provided the briefing material supplied to its representatives regarding the abstract.

PANEL RULING

The Panel noted that the printed abstract had additional information, regarding the comparative costs of Abelcet and AmBisome, handwritten at the bottom of the page. The information showed a price advantage for AmBisome. In the Panel's view the abstract had been used to promote AmBisome. The additional data had been taken from incorrect information which had been presented at the American Society for Haematology Annual Meeting. The Panel considered it unfortunate that there had been errors in the information presented but noted that, under the Code, pharmaceutical companies were responsible for the accuracy of promotional material. The price information was misleading and a breach of Clause 7.2 of the Code was ruled.

The Panel noted that the handwritten information regarding prices had turned the abstract into a piece of promotional copy for AmBisome. Prescribing information should thus have been included. There was no prescribing information for AmBisome included. The Panel noted that there was no allegation regarding the lack of prescribing information but requested that NeXstar's attention be drawn to the requirements of Clause 4.1 of The Code

Complaint received 29 July 1998

Case completed 24 September 1998

CASE AUTH/750/8/98

CONSULTANT CHEST PHYSICIAN v GLAXO WELLCOME

Promotion of Flixotide

A consultant physician complained about the promotion of Flixotide (fluticasone) by Glaxo Wellcome, submitting two journal advertisements as examples. The complainant said that Flixotide was promoted consistently as having greater efficacy than other inhaled steroids, the comparison nearly always being with budesonide, but this was clearly not the case. The efficacy of all the inhaled steroids was the same and no studies had ever shown anything different. There was a clear attempt to mislead general practitioners.

The Panel noted that the advertisements included the claims "Flixotide given at half the daily dose of budesonide was more effective than budesonide at improving mean percent predicted morning peak flow" and "Flixotide Accuhaler 100 micrograms b.d. has an efficacy advantage over budesonide turbo inhaler 200 micrograms b.d."

The Panel noted that the summary of product characteristics (SPC) for Flixotide stated that "Equivalent disease control is usually obtained at half the daily dose of other currently available inhaled steroids". The British Guidelines on Asthma Management stated that fluticasone was as effective as beclomethasone and budesonide at half the dose when given by equivalent delivery systems and that at equivalent doses fluticasone might have the potential for producing similar systemic effects to those of beclomethasone and budesonide. The Panel considered that the claims in the advertisements, in relation to the effects of Flixotide when given at half the daily dose of budesonide, were not unreasonable. Glaxo Wellcome had provided data to support the claims. The first claim referred to the particular advantage - improving mean percent predicted morning peak flow. The second claim referred to particular doses of the products and claimed "an efficacy advantage". Although it might have been helpful to give more detail about the efficacy advantage, the Panel considered that, on balance, the claims were not misleading. No breach of the Code was ruled.

Upon appeal by the complainant, the Appeal Board considered that the claim "Flixotide given at half the daily dose of budesonide was more effective than budesonide at improving mean percent predicted morning peak flow" was a very general claim. While it was clear that the advertisement related to the treatment of asthma in children there was no mention of either the doses or the devices used. The implication was that the claim was true for all doses and all devices. There was no data to support this implication. The Appeal Board considered that the claim was misleading and a breach of the Code was ruled. The Appeal Board considered that the claim "Flixotide Accuhaler 100 micrograms b.d. has an efficacy advantage over budesonide turbo inhaler 200 micrograms b.d." was not unreasonable. It was clear that the subject was the treatment of asthmatic children. The Appeal Board did not consider that the claim was misleading and upheld the Panel's ruling of no breach of the Code. The Appeal Board considered that the claim "Flixotide at half the daily dose has demonstrated more treatment successes than budesonide for only a few pence more per day" was misleading. The claim could be read that Flixotide at half its daily dose demonstrated more treatment successes than budesonide and not that the daily dose of Flixotide was half the daily dose of budesonide. The Appeal Board ruled a breach of the Code.

It was also alleged that the claim "In addition Flixotide has no effect on growth at recommended doses" could not be made in relation to any inhaled steroid. The Panel noted that the claim in question referred to "recommended doses" which Glaxo Wellcome had submitted would be read to mean "doses described in the prescribing information" ie in children aged 4 and over, 50 to 100mcg twice daily. The British Guidelines

on Asthma Management referred to doses of 1000 micrograms per day for school children. In the Panel's view, although it might have been helpful to give more information about the recommended doses in the body of the advertisement, particularly given the wide use of the British Guidelines on Asthma Management, the claim was not unacceptable. The Panel did not consider that the claim was misleading. At the time of publication it had been consistent with the Flixotide SPC. No breach of the Code was ruled.

A consultant chest physician complained about the promotion of Flixotide (fluticasone) by Glaxo Wellcome UK Limited. Two sample journal advertisements were provided (refs GEN 25409/January 1998 and GEN24775).

1 Flixotide was promoted consistently as having greater efficacy than other inhaled steroids, the comparison nearly always being with budesonide.

COMPLAINT

The complainant stated that the situation was that this was clearly not the case. The efficacy (ie maximum effect that could be achieved with the medicine) of all the inhaled steroids was the same, as it was indeed with the oral steroids hydrocortisone, prednisolone and dexamethasone, and there were no studies that had ever shown anything different. There were, however, differences in potency between the inhaled steroids, but these of course were irrelevant for the therapeutic effect. There was a clear attempt to mislead general practitioners and asthma nurses that Flixotide was more effective than other steroids.

The complainant provided articles from Prescriber's Journal and Current Problems in Pharmacovigilance which warned doctors against being confused between the difference between potency and efficacy, the latter with specific reference to inhaled steroids.

RESPONSE

Glaxo Wellcome stated that it was aware that Clause 7.2 of the Code specifically warned against claims which related solely to differences in potency in relation to weight.

It was well accepted that there might be differences between the potency of different molecules of the same class. Potency might be measured in an experimental model which might not be directly related to the desired therapeutic effect. Such was the case with fluticasone, which was more potent than other currently available corticosteroids when measured in experimental models for its glucocorticoid receptor affinity and rates of association and dissociation. When tested in *in vitro* systems for effects upon cellular function then fluticasone was also more potent. *In vitro* potency might be highly pertinent when it was related to the concentrations of the active drug which were achieved in the relevant tissues or organs during clinical use.

The efficacy of all inhaled corticosteroids was not the same. The effects of any medicines of a particular class would depend upon the properties of the medicine, the receptor, the given tissue and its receptor density and how receptor occupancy by the medicine related to the ultimate effect. Hence the concept of "maximal efficacy", which represented the plateau of the concentration-effect curve. According to the complainant the term "efficacy" was the maximum effect, which was not compatible with this concept. In clinical practice, different drugs had different concentration:effect curves, with the result that the same microgram doses of those different drugs would yield different outcomes. The plateaux of those curves would also be at different levels. An added factor in practice was that the product licence might limit the upper dose of a medicine, in order to balance efficacy against the safety profile.

To illustrate differences in efficacy in clinical practice required patients who remained capable of demonstrating further benefit. For example, the double blind, parallel group study by Ayres *et al* (1995) in 671 patients with chronic severe asthma compared the effects of inhaled budesonide 800mcg bd with two doses of fluticasone, namely 500mcg bd and 1000mcg bd over six weeks. While all treatments increased the mean peak expiratory flow (PEF), the mean morning PEF and % predicted mean morning PEF were increased statistically significantly more in the two groups of patients taking fluticasone than in those taking budesonide at its maximum recommended dose. This suggested that within the recommended dosage ranges of the two drugs the efficacy of fluticasone was greater than that of budesonide.

Another double blind, parallel group study, by Ringdal *et al* (1996) in 518 patients with moderate to severe asthma compared the effects of fluticasone 400mcg bd via Diskhaler with budesonide 800mcg bd via Turbohaler (maximum licensed dose) over 12 weeks. Again there were statistically significant differences in favour of the patients taking fluticasone, in terms of mean morning and evening PEF and other parameters of lung function. This again indicated that within recommended dosage ranges, fluticasone was more efficacious than budesonide. That was to say that there were patients who would benefit from fluticasone when they might no longer show further improvement on budesonide, certainly within the recommended dosage range of the latter medicine.

This efficacy advantage had been linked to other features of fluticasone, such as the greater likelihood of achieving a successful outcome, but at very little difference in cost, compared with budesonide. The meta-analysis of studies by Barnes *et al* (1998) suggested that when inhaled fluticasone was used at half the dose of budesonide or less, at doses of the latter up to 800mcg bd there was a likelihood of a greater increase in mean morning PEF and a likelihood of there being less effect upon mean morning plasma cortisol with fluticasone than with budesonide.

In one advertisement, the statement relating to efficacy was also linked to the statement derived from the same supporting study that children in that study "rated the Flixotide Accuhaler more highly than the budesonide turbulent-flow reservoir powder device", which was an important consideration when prescribing an inhaler device, especially for a child.

PANEL RULING

The Panel noted that there was a difference between efficacy and potency. The supplementary information to Clause 7.2 of the Code stated that "claims for superior potency in relation to weight are generally meaningless and best avoided unless they can be linked to some practical advantage...". The Panel noted the specific allegation that Flixotide was consistently promoted as having greater efficacy than inhaled steroids, the comparison nearly always being with budesonide. Each advertisement had to be considered on its individual merits. The Panel noted that the advertisements included claims "Flixotide given at half the daily dose of budesonide was more effective than budesonide at improving mean percent predicted morning peak flow" (ref GEN24775) and "Flixotide Accuhaler 100 micrograms b.d. has an efficacy advantage over budesonide turbo inhaler 200 micrograms b.d." (ref GEN 25409/January 1998). Both claims were referenced to Williams *et al* 1997.

The Williams *et al* study had compared the ease of handling and clinical efficacy of fluticasone Accuhaler/Diskus with the budesonide Turbohaler. The study had been carried out in 323 children aged 4-11 years. The primary efficacy parameter was mean percent predicted morning peak flow. The mean percent predicted morning PEF for the whole four week treatment period was higher in the fluticasone Accuhaler group ($p=0.012$). When the mean predicted morning PEF at week 4 alone was compared to the baseline week the increase in the fluticasone group was statistically significant compared to the increase in the Turbohaler group ($p=0.0003$). There were no statistically significant differences between groups for any of the other efficacy parameters, diurnal variation, symptom-free days and nights and relief medication-free days and nights although numerically all were in favour of the fluticasone group. The study was the first comparing fluticasone via Accuhaler with budesonide via the Turbohaler in children.

The Panel noted that the summary of product characteristics (SPC) for Flixotide stated "Equivalent disease control is usually obtained at half the daily dose of other currently available inhaled steroids".

The British Guidelines on Asthma Management stated that fluticasone was as effective as beclomethasone and budesonide at half the dose when given by equivalent delivery systems. At equivalent doses fluticasone might have the potential for producing similar systemic effects to those of beclomethasone and budesonide.

The Panel considered that the claims in the sample advertisements in relation to the effects of Flixotide when given at half the daily dose of budesonide were not unreasonable. Glaxo Wellcome had provided data to support the claims. The first claim referred to the particular advantage - improving mean percent predicted morning peak flow. The second claim referred to particular doses of the products and claimed "an efficacy advantage". Although it might have been helpful to give more detail about the efficacy advantage, the Panel considered that on balance, the claims were not misleading. No breach of Clause 7.2 of the Code was ruled.

APPEAL BY THE COMPLAINANT

The complainant repeated again that it had never been shown that there was any difference in efficacy between the inhaled steroids. The definition of efficacy as the maximum effect obtainable with a particular medicine was commonly accepted in standard tests. There was no study that had ever shown that the maximum effect of fluticasone was greater than any other inhaled steroid. The studies quoted by Glaxo Wellcome compared budesonide and fluticasone at dosages which might not be equipotent. The potency relationships between fluticasone versus budesonide and beclomethasone in their different inhaling devices might be approximately 2:1, but differed between inhaling devices and could only be calculated precisely by dose response studies for each medicine/device system (Pedersen and O'Byrne, 1997). Unfortunately, there was only one such study (beclomethasone metered dose inhaler (MDI) versus fluticasone MDI) and the potency relationship between the other steroid/device systems could only be approximated. In other words, in the studies quoted by Glaxo Wellcome, if the dosage of budesonide had been increased the same effect would have been achieved compared with the given dosage of fluticasone. All that the studies quoted demonstrated was a potency difference between two inhaled steroids. To demonstrate a true difference in efficacy, a dose response curve for each inhaled steroid should be constructed, and the plateau of maximum effect compared. No such study existed.

The complainant noted the claims in the Flixotide advertisements - "Flixotide given at half the daily dose of budesonide was more effective than budesonide", and "Flixotide Accuhaler has an efficacy advantage over budesonide Turbohaler". The intention was clearly to convince that fluticasone was more effective than budesonide in much the same way as insulin was more effective than oral hypoglycaemics in diabetics. To demonstrate how misleading this type of product advertising was the complainant drew a parallel: The diuretics bumetanide and frusemide had equal efficacy but a difference in potency. 1mg of bumetanide and 40mg of frusemide were exactly equipotent doses. A study was constructed which compared 2mg of bumetanide with 40mg of frusemide. The subsequent claims were "Bumetanide at one twentieth the daily dose of frusemide was more effective than frusemide at increasing urinary output" and "Bumetanide has an efficacy advantage over frusemide". The complainant submitted that there would only be one purpose for making such claims - to persuade doctors that bumetanide was to be preferred because it was more effective. This would, of course, be misleading and untrue - but what was the difference between this and the present promotion of Flixotide? If this type of marketing was permitted, it would set a precedent for other pharmaceutical companies' products.

The complainant submitted that there might be many good reasons for prescribing Flixotide in preference to other inhaled steroids, but greater efficacy was not one of them.

The complainant queried that to prevent false or misleading claims for greater efficacy for any medicine, surely the pharmaceutical company must substantiate such claims by showing response studies indicating that

the plateau of maximum effect for their medicine was superior to competitors?

The complainant provided references to support the appeal. The complainant pointed out that the references supplied with the appeal were from completely independent sources. The studies supplied by Glaxo Wellcome were all sponsored by Glaxo Wellcome.

RESPONSE BY GLAXO WELLCOME

Glaxo Wellcome noted that in its ruling, the Panel had noted that each advertisement had be considered on its individual merits. Both the company and the Panel had agreed that there was a difference between efficacy and potency. In relation to the claims in the advertisements in question, Glaxo Wellcome found it hard to understand the complainant's point in relation to the matters being considered.

Glaxo Wellcome still considered that its original submission stood but would try to address the complainant's points later in its response to the appeal. However, the company dealt with the specific claims from the advertisements in turn.

"Flixotide Accuhaler 100 micrograms b.d. had an efficacy advantage over budesonide turbo inhaler 200 micrograms b.d."

Glaxo Wellcome submitted that this was a reasonable claim, based upon the results of the study by Williams and Richards, which compared fluticasone 100 micrograms bd by Accuhaler with budesonide 200 micrograms bd by turbo inhaler and which was cited in its support. In this study, in 323 children aged 4-11 years, most parameters showed no significant difference between the two groups. However, there was a significant difference ($p = 0.0003$), in favour of the fluticasone group in the improvement in mean morning, percent predicted peak expiratory flow (PEF) over four weeks, which was the primary outcome variable for the study. Hence the statement "efficacy advantage", which Glaxo Wellcome considered was a rather subdued claim and reflected the facts of the case.

"Flixotide at half the daily dose has demonstrated more treatment successes than budesonide for only a few pence more per day"

Glaxo Wellcome stated that this was another claim based upon the Williams and Richards study referred to above. In this study, an analysis was performed in which "treatment success" was defined as an improvement in predicted PEF of at least 5% and this was explained as a footnote to the advertisement. On this basis, the use of fluticasone 100 micrograms bd via the Accuhaler was more likely to result in "treatment success" than the use of budesonide 200 micrograms via turbo inhaler. In fact, this would have been the case whatever per cent improvement in predicted PEF had been chosen. Again, the company considered that the claim simply reflected the results of the study and even accepted that it might cost a little more to achieve this greater likelihood of success.

"Flixotide given at half the daily dose of budesonide was more effective than budesonide at improving mean percent predicted morning peak flow."

Glaxo Wellcome stated that this claim expressed the same result regarding the change in PEF which had been demonstrated in the study by Williams and Richards. As explained in the company's original response, the advertisement also stated another finding of this study which was that "children rated the Flixotide Accuhaler more highly than the budesonide Turbohaler-flow reservoir powder device." Glaxo Wellcome considered that this was a very important consideration when prescribing an inhaler device to a child.

Glaxo Wellcome stated that in its original response it had supported the findings in this paediatric study by citing the meta-analysis of studies by Barnes *et al.* This had suggested that when fluticasone was used at half the dose of budesonide or less, at doses of the latter up to 800 micrograms bd there was a likelihood of a greater increase in mean morning PEF and a likelihood of there being less effect upon mean morning plasma cortisol with fluticasone than with budesonide.

Glaxo Wellcome did not consider that much of what the complainant had written was relevant. In the original response the company had made the point that it had to make comparisons between medicines within the range of their licensed doses. There was evidence as quoted in that response that greater benefits could be obtained with Flixotide than with budesonide, for example, within their licensed doses. The licensed dosage range took into account the balance between clinical, desired efficacy and unwanted effects. This was well illustrated in the enclosed papers from the complainant, in which the frusemide:bumetanide example was highlighted and was used in the complainant's own letter. What was not highlighted was the statement in the next column that two medicines might be equipotent in one respect or system but might differ in another. The example quoted was that doses of bumetanide and frusemide might have equivalent effects on urinary sodium excretion but bumetanide was less ototoxic and so might be preferred in some situations.

Glaxo Wellcome stated that it did not agree that when specific comparisons were made between two medicines it should be necessary to show extensive dose response studies, which were themselves only applicable within that particular study population.

The company was very unhappy to read the note from the complainant that implied that Glaxo Wellcome sponsored studies might not be valid.

Glaxo Wellcome noted that of the "completely independent texts" which had been supplied by the complainant: Professor B J Lipworth had published several studies which had compared fluticasone with budesonide and at least three of the studies acknowledged support for those studies or for individual investigators from the Astra Foundation. The "Allergy" supplement by Professors Soren Pedersen and Paul O'Byrne was sponsored by Astra Denmark, although the sponsorship was not acknowledged in the publication.

In conclusion therefore, Glaxo Wellcome reiterated its previous defence of the complaints in this case and hoped the additional comments in this response further clarified the issues.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant summarised the situation thus:

1 Part of the marketing strategy for Flixotide was to claim better efficacy. Thus, in the two advertisements considered, the phrases "efficacy advantage" and "was more effective than".

2 True differences in efficacy could only be proven by demonstrating a difference in maximum effect (Prescriber's Journal 1997) which Glaxo Wellcome could not do. The British Thoracic Society Guidelines (1997) did not advise that any other inhaled steroid was more effective than any other - "The relative merits of newly introduced inhaled corticosteroids compared with those of long standing remain to be demonstrated".

The complainant stated that the Medicines Control Agency and the Committee on Safety of Medicines had also expressed concern on the issue of better efficacy claims - "Greater potency does not, however, necessarily equate with greater efficacy". (Current Problems in Pharmacovigilance 1998).

3 Glaxo Wellcome continually referred to the meta-analysis of studies by Barnes *et al* (co-written and sponsored by Glaxo Wellcome) and published in Respiratory Medicine to support its claims. The complainant provided a copy of a letter he had sent to the publishers of Respiratory Medicine. It was his contention that this paper had no scientific content and was misleading The complainant noted that the journal's publisher viewed the issues raised in the letter "with great concern", and had accepted the letter for publication.

The complainant stated that the differences in potency between the inhaled corticosteroids were irrelevant to therapeutic effect. They only mattered when considering cost effectiveness or safety (ie better therapeutic index). Claims for "efficacy advantage" or being "more effective" were unsubstantiated and deliberately misleading.

The complainant stated that the Prescriber's Journal, the British Thoracic Society Guidelines, the Medicines Control Agency and the Committee on Safety of Medicines had all commented on, or expressed concern on the issue. Could the Authority not control advertising that falsely misrepresented simple potency differences as being advantageous? If it did not would this send the wrong signal to the rest of the industry?

APPEAL BOARD RULING

In response to a question, Glaxo Wellcome's representative confirmed that the advertisement headed "An inhaled steroid to grow up with" which included the claims "Flixotide given at half the daily dose of budesonide was more effective than budesonide at improving mean percent predicted morning peak flow" had been used from March 1997 until March 1998. The advertisement headed "Flixotide is five" which included the claims "Flixotide Accuhaler 100 micrograms b.d. has an efficacy advantage over budesonide turbo inhaler 200 micrograms b.d." and "Flixotide at half the daily dose has demonstrated more treatment successes than budesonide for only a few pence more per day" had been used from March 1998 until August. The Medicines Control Agency (MCA) had reviewed the SPCs and data sheets for inhaled and nasal corticosteroids and amendments had been made. The representative stated that his understanding was that in future comparisons of such products would need to include the doses, devices and details of the patient group.

The Appeal Board noted that the advertisements in question had to be considered in the light of information available at the time they were used. The Appeal Board noted the statement in the Flixotide SPC that equivalent disease control was usually obtained at half the daily dose of other currently available inhaled steroids.

The Appeal Board considered that the claim "Flixotide given at half the daily dose of budesonide was more effective than budesonide at improving mean percent predicted morning peak flow" was a very general claim. While it was clear that the advertisement related to the treatment of asthma in children there was no mention of either the doses or the devices used. The implication was that the claim was true for all doses and all devices. There was no data to support this implication. The study to which the claim was referenced, Williams and Richards (1997), was the only study to compare the use of an Accuhaler and a turbo inhaler in children and used daily doses of fluticasone (via Accuhaler/Diskus) of 200mcg and budesonide (via a turbo inhaler) of 400mcg. The Appeal Board considered that the claim was misleading and a breach of Clause 7.2 of the Code was ruled.

The appeal on this point was successful.

The Appeal Board considered that the claim "Flixotide Accuhaler 100 micrograms b.d. has an efficacy advantage over budesonide turbo inhaler 200 micrograms b.d." was not unreasonable. The claim was referenced to the Williams and Richards study which had shown that 200mcg of Flixotide via Accuhaler was more effective than budesonide 400mcg daily via the turbo inhaler in terms of mean percent predicted morning peak expiratory flow. It was clear that the subject was the treatment of asthmatic children. The Appeal Board did not consider that the claim was misleading and upheld the Panel's ruling of no breach of Clause 7.2 of the Code.

The appeal on this point was unsuccessful.

The Appeal Board considered that the claim "Flixotide at half the daily dose has demonstrated more treatment successes than budesonide for only a few pence more per day" was misleading. The claim could be read that Flixotide at half its daily dose demonstrated more treatment successes than budesonide and not that the daily dose of Flixotide was half the daily dose of budesonide. The Appeal Board ruled a breach of Clause 7.2 of the Code.

The appeal on this point was successful.

2 Claim "In addition Flixotide has no effect on growth at recommended doses"

This claim appeared in only one of the advertisements submitted (ref GEN 25425409/January 1998)

COMPLAINT

The complainant stated that the claim could not be made in relation to any inhaled steroid. Some children were sensitive to even small amounts of inhaled steroids and had retarded growth. The complainant provided two case histories where children developed growth retardation when on Flixotide at doses within the product licence. Further, the advertisement did not make clear what 'recommended doses' were. Did it mean within the product licence? Did it mean within the British Guidelines on Asthma Management doses?

Product licence dosage in children was 200mcg/daily, but the Guidelines allowed up to 1000mcg/daily for children of school age. The complainant had reported to the Committee on Safety of Medicines more than 10 cases of children with severe asthma who had had severe retardation of growth at 1000mcg per day. Several of these cases were reported in The Lancet and details were provided.

The complainant suggested that the claim: "In addition, Flixotide has no effect on growth at recommended doses," should read: "In addition, Flixotide is unlikely to have any effect on growth at doses of 200mcg per day or less."

RESPONSE

Glaxo Wellcome submitted that when the claim was made, it was qualified by reference to four studies of at least 12 months' duration. In none of these was there evidence of an effect on growth in the children studied. Glaxo Wellcome still believed this to be the case.

The complainant had enclosed a copy of a report from Zimmerman *et al* of a 9-year old child who had been treated with beclomethasone, budesonide and fluticasone. The latter was prescribed in a dosage of 250mcg/daily by MDI which was outside the maximum recommended daily dose for children between 4 and 16 years, which was 200mcg/daily. With such a brief history it was difficult to be certain about the actual dose of fluticasone that might have been taken, especially as the patient had previously been instructed to double the dose of budesonide in the event of viral infections. The second case in the attached case reports was of a 32 year old woman which was not relevant to a discussion on growth

The complainant had stated that the "recommended dose" was not made clear on the advertisement, but the prescribing information was clearly a part of the enclosed advertisements, with recommendations which had not changed since the launch of Flixotide in 1993: "...Children aged 4 and over: 50 to 100 micrograms twice daily." Glaxo Wellcome submitted that it could only promote within the terms of its product licence and it was evident from the advertisements that this was the case. The recommendations of the British Guidelines on Asthma Management had been a useful source of advice for the prescribing doctor, but they were drawn up by a group of independent experts and reflected clinical experience and the weight of published evidence available at the time. Occasionally, the recommendations of such guidelines might be outside those of the product licence and Glaxo Wellcome could not associate itself with such dosage recommendations.

Glaxo Wellcome was aware that cases of adrenal suppression and growth restriction had been reported by Todd *et al* (1996) in a paper in The Lancet, in children with asthma who had been treated with doses of Flixotide between 5 and 11 times the maximum recommended dose. Glaxo Wellcome had not linked its statement about "no effect on growth" with doses outside its licence, so it hardly considered that the experience of Todd *et al* was relevant to its advertising.

Glaxo Wellcome noted that, while all the data sheets and SPCs for all companies' inhaled and intra-nasal corticosteroids had recently undergone revision, at the time of publication the advertisements were in line with the SPC for Flixotide. All future advertising and promotional materials would be reviewed in the light of the class effect wording recently agreed with the MCA.

PANEL RULING

The Panel noted that Clause 3.2 of the Code required that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its SPC or data sheet. Companies had been, and would be, ruled in breach of Clause 3.2 for referring to unlicensed doses in their advertising.

The Panel noted that The British Guidelines on Asthma Management referred to doses of fluticasone of 1000 micrograms per day for school children whereas the licensed dose for Flixotide for children aged 4 and over was 50 to 100 micrograms twice daily. The Guidelines referred to the need to measure children's height on a regular basis and that impaired growth was one of the signs of uncontrolled asthma as well as being a potential side effect of steroid therapy. The Flixotide SPC stated that "Some biochemical changes reported in children, but no stunting of growth observed." The Panel noted that the Guidelines were well known and used by health professionals

The Panel noted that corticosteroids had been the subject of a recent edition of Current Problems in Pharmacovigilance issued by the CSM and the MCA. This included an article discussing the safety of inhaled and nasal corticosteroids. Reference was made to growth retardation being reported in children receiving nasal corticosteroids at licensed doses. It was recommended that the height of children receiving prolonged treatment with inhaled or nasal corticosteroids was regularly monitored. The article also stated that the recognition that systemic effects might occur, and that the lowest effective dose should be used, did not alter the favourable risk-benefit profile of inhaled and nasal corticosteroids.

The Panel noted that the claim in question referred to "recommended doses" which Glaxo Wellcome submitted would be read to mean 'doses described in the prescribing information' ie in children aged 4 and over, 50 to 100mcg twice daily. In the Panel's view, although it might have been helpful to give more information about the

recommended doses in the body of the advertisement, particularly given the wide use of the British Guidelines on Asthma Management, the claim was not unacceptable. The Panel did not consider that the claim was misleading, at the time of publication it was consistent with the Flixotide SPC and no breach of Clause 7.2 of the Code was ruled.

The Panel noted that, since the publication of the advertisement in question there had been revisions to all SPCs and data sheets for inhaled and nasal corticosteroids. Glaxo Wellcome had stated that all future promotion would be reviewed in the light of the class effect wording recently agreed with the MCA.

Complaint received 3 August 1998

Case completed 14 December 1998

CASES AUTH/752/8/98 AND AUTH/753/8/98

BRISTOL-MYERS SQUIBB and SANOFI WINTHROP v ASTRA and TAKEDA

Promotion of Amias

Bristol-Myers Squibb and Sanofi Winthrop complained about several statements made in an Amias information pack, detail aid and journal advertisement issued by Astra and Takeda.

Section 6.7 of the information pack entitled "Cardiac hypertrophy and congestive cardiac failure" was alleged to promote Amias for an unlicensed indication. Amias (candesartan) was indicated for the treatment of essential hypertension. The section discussed the favourable results of two studies one of which, Matsumori *et al*, examined the efficacy and safety of Amias in the treatment of mild to moderate chronic heart failure. It was also alleged that an implication that Amias was of benefit in patients with hypertension and concomitant congestive heart failure on the basis of the data provided was not balanced or accurate.

The Panel considered that too much information had been given on the use of Amias in an unlicensed indication, heart failure, and a breach of the Code was ruled. In addition the Panel made certain comments about the description of the study in the information pack. A breach of the Code was ruled as the information pack did not accurately reflect the summary of product characteristics.

It was also alleged that Section 6.7 of the information pack was misleading as it stated that the medicine was well tolerated in chronic heart failure but did not include any information about the RESOLVD study, the largest heart failure study conducted with Amias which was stopped prematurely due to an increased mortality rate in patient groups which received Amias alone or Amias and an ACE inhibitor.

The Panel noted that the information pack had been prepared in December 1997. The data from the RESOLVD study had been published in November 1997. The trial was not powered to show an effect on clinical events and death. The Panel noted that after the trial was halted an analysis of the data showed that differences between the three patient groups with regard to death rates and hospitalisation were not statistically significant. The study was neither aimed nor powered to detect an effect on clinical events or death. The Panel considered that in the circumstances it was reasonable not to refer to mortality data from the RESOLVD study and ruled no breach of the Code.

Bristol-Myers Squibb and Sanofi alleged that the claim in the detail aid "Am I as ... outstanding in the treatment of hypertension?" adjacent to a visual of a tall building surrounded by shorter buildings implied that Amias was outstanding and was an exaggerated claim in breach of the Code.

The Panel noted previous cases (AUTH/666/1/98 and AUTH/667/1/98) where no breach of the Code had been ruled in relation to a journal advertisement. The front page of the detail aid now at issue was different to the journal advertisement. Unlike the earlier advertisement there was no discussion of the clinical features of Amias and the answer to the question on the front page was not addressed by the content of the detail aid. The Panel considered that the front page of the detail aid implied that Amias was outstanding in the treatment of hypertension and a breach of the Code was ruled.

A claim in the detail aid "Am I a smooth acting anti-hypertensive?" and accompanying histogram entitled "A high trough-to-peak ratio indicates consistent 24 hour effect" were alleged to be misleading and unfair. The histogram placed angiotensin II receptor antagonists (AIIRAs) in descending order of magnitude with reference to their trough-to-peak (T:P) ratios. Each product depicted had a T:P ratio of at last 60%. The data points for the comparison were derived from four different studies and the histogram implied a special merit for Amias. Equivalent doses of AIIRAs had not been established and the clinical significance of a T:P ratio of over 50% was not known.

The Panel considered that the histogram and claim "High trough-to peak ratio indicates consistent 24 hr effect" created the impression that the T:P ratios based on the stated doses were directly comparable and that Amias with a T:P ratio of 80-100% would be a smoother acting antihypertensive than the other AIIRAs. A breach of the Code was ruled.

The Panel also ruled a breach of the Code as the impression from the histogram was that the data was from a comparative study and this was not so.

It was also alleged that a picture of the world cup trophy and claim that Amias was a crowd pleaser in the journal advertisement implied a superiority for Amias which constituted an exaggerated claim and a special merit that could not be substantiated. The Panel did not accept that the references to the world cup trophy constituted an exaggerated claim and no breach was ruled. The Panel did not accept that the material inferred that Amias was the winning treatment, merely a winning treatment for hypertension. No breach of the Code was ruled.

Bristol-Myers Squibb Pharmaceuticals Ltd and Sanofi Winthrop Limited submitted a complaint about the co-promotion of Amias (candesartan) by Astra Pharmaceuticals Ltd and Takeda UK Ltd. The complaint concerned claims made in an Amias information pack (AMS 2346/3486), detail aid (AMS 2842) and journal advertisement (AMS 3326/TA80310).

Astra and Takeda submitted identical responses to the complaint.

1 Amias Information Pack

The information pack was used in response to enquiries for detailed background information on the product. Section 6 of the information pack discussed the use of Amias in special patient groups. The complaint concerned Section 6.7 entitled "Cardiac hypertrophy and congestive cardiac failure", which read:

> "An assessment, with magnetic resonance imaging and echocardiography in hypertensive patients, found that the main haemodynamic effects after Amias treatment for 8-12 weeks were a reduction in blood pressure and a regression in left ventricular hypertrophy. Amias had no significant effect on heart rate, stroke volume or cardiac output, nor any effect on other measures of left ventricular function (including left ventricular end-diastolic- or end-systolic-volumes, left ventricular ejection fraction, and dp/dt) [Mitsunami *et al* (1994)]
>
> Inhibition of the renin-angiotensin-aldosterone system by ACE-inhibitors has been shown to be beneficial in patients with heart failure.
>
> Amias 0.5-4mg was well tolerated in patients with chronic heart failure and patients showed improvements in clinical condition and left ventricular function (dimensions and ejection fraction) after treatment [Matsumori *et al* (1995)]. This indicates that haemodynamic problems are not likely if these doses of Amias are used in patients with hypertension and concomitant congestive heart failure. The possible benefits of candesartan in this patient group are under investigation. Amias is not licensed for treatment of heart failure".

a Allegation that promotion inconsistent with the product licence

COMPLAINT

Bristol-Myers Squibb and Sanofi alleged that the link from the second to the last paragraph of Section 6.7 implied that the benefits that resulted from treatment of chronic heart failure (CHF) with ACE inhibitors, due to their action on the renin-angiotensin-aldosterone system, could be extrapolated to candesartan. The literature on this issue was more complex that the piece implied.

Candesartan was only licensed to treat hypertension. Although the section in question stated that candesartan was not licensed for the treatment of CHF, the information on the use of candesartan in CHF was presented in order to suggest to physicians that they should consider this medicine as a well tolerated alternative to ACE inhibitors. Bristol-Myers Squibb and Sanofi noted that this was not consistent with the product licence and therefore alleged a breach of Clause 3.2 of the Code.

RESPONSE

Astra and Takeda stated that the statement about the use of ACE inhibitors introduced the rationale for investigating the use of angiotensin II receptor antagonists (AIIRAs) in patients with heart failure and provided evidence that one class of medicine acting on the renin-aldosterone-angiotensin system had been shown not to have deleterious effects in this patient group. This was relevant because antihypertensives acting in other ways (for example, beta-blockers) might worsen heart failure. The statement most certainly did not imply that the benefits of ACE inhibitors in the treatment of heart failure could be extrapolated to Amias.

Section 6 of the information pack covered the use of Amias in special patient groups of hypertensive patients. Section 6.7 covered the use of Amias in hypertensive patients with concomitant heart failure. It was clearly stated that Amias was not licensed for the treatment of heart failure. The allegation that the information was presented in order to suggest to physicians that they should consider Amias as a well tolerated alternative to ACE inhibitors in heart failure was unfounded.

Astra and Takeda denied the alleged breach of Clause 3.2 of the Code.

PANEL RULING

The Panel examined the summary of product characteristics (SPC) for Amias which stated that it was indicated for treatment of essential hypertension. The suggested starting dose was 4mg once daily. The usual maintenance dose was 8mg once daily. In elderly patients with impaired hepatic function an initial dose of 2mg was recommended. In a section headed 'Special warnings and special precautions for use' it stated that special caution was indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy. The subsection headed "General" referred to the fact that in those patients whose vascular tone and renal function depended predominantly on the activity of the renin-angiotensin-aldosterone system (for example patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis) treatment with other medicines that affected this system had been associated with acute hypotension, azotaemia, oliguria, or rarely, acute renal failure. Although the possibility of

similar effects could not be excluded with angiotensin II receptor antagonists, these effects were not reported with Amias.

The Panel noted the submission that the purpose of Section 6.7 in the information pack was to show that in patients with hypertension and concomitant congestive heart failure, treatment with Amias was unlikely to produce haemodynamic problems.

The section discussed the favourable results of two studies. Mitsunami *et al* (1994) which examined the main haemodynamic effects after Amias treatment in hypertensive patients and Matsumori *et al* (1995) which examined the efficacy and safety of Amias in patients with chronic heart failure. The section referred to the unlicensed dosage (0.5 - 4mg) used in the Matsumori study.

In the opinion of the Panel the section in the information pack contained more than a simple statement of fact about the haemodynamic effect of Amias in a particular patient group. Discussion of the work by Matsumori included reference to specific doses and clinical results in patients with heart failure. In the Panel's view too much information had been given on the use of Amias in heart failure. A breach of Clause 3.2 of the Code was ruled.

b Use of the Matsumori study

COMPLAINT

Bristol-Myers Squibb and Sanofi stated that the implication that Amias was of benefit in patients with hypertension and with concomitant CHF, on the basis of the data provided, was not balanced or accurate.

The Matsumori study included patients with chronic heart failure and without concomitant hypertension. However the third paragraph of section 6.7 claimed that candesartan would be well tolerated in patients with CHF and concomitant hypertension - a claim that could not be supported by the evidence presented.

Bristol-Myers Squibb and Sanofi alleged that furthermore, linking this "benefit" to hypertensive patients was a device - used in this piece in order to make a safety claim about the use of the product in treating patients with hypertension. This represented a claim which misled by implication as very few patients with hypertension, for which candesartan was approved for use, had concomitant CHF, therefore the generality of the data presented was limited.

Breaches of Clauses 3.2 and 7.2 were alleged.

RESPONSE

Astra and Takeda stated that contrary to the complainants' statement that very few patients with hypertension had concomitant CHF, it was well known that heart failure and hypertension often coexisted and that hypertension was one of the major risk factors for developing chronic heart failure. The sub-group of hypertensive patients which progressed to heart failure had a high mortality and was therefore extremely important to clinicians.

The section outlined the findings of the Matsumori study in patients with chronic heart failure. Whilst blood pressure status was not confirmed in this study, the findings of lack of effect on haemodynamic parameters was relevant given the known association between CHF and hypertension. On this basis it stated in this section that low doses of Amias were unlikely to cause haemodynamic problems in hypertensive patients with concomitant congestive heart failure.

Astra and Takeda submitted that the section did not mislead by implication; there was no attempt made to generalise the information as it was quite clearly focused on hypertensive patients with concomitant heart failure. Indeed, it formed part of a larger section of the information pack headed Special Patient Groups.

PANEL RULING

The Panel considered that its ruling in point 1a above that too much information had been given on the use of Amias in heart failure and the section amounted to the promotion of an unlicensed indication in breach of Clause 3.2 of the Code was relevant to the allegation it was now considering.

The Panel noted that the Matsumori study assessed the efficacy and safety of Amias in 77 patients with chronic heart failure. The doses used were 0.5mg, 1mg, 2mg and 4mg. The study concluded that Amias was useful in the treatment of mild to moderate chronic heart failure at a daily dose of 2mg or 4mg. The Panel noted that the blood pressure status of the patients in the Matsumori study was not given.

In the opinion of the Panel the discussion of the results of the Matsumori study in the information pack implied that Amias was well tolerated and of benefit in patients with hypertension and concomitant heart failure. The Panel noted that the discussion of the Matsumori study in the information pack did not state that patients had mild to moderate heart failure. In the Panel's opinion the information pack implied that Amias was well tolerated in hypertensive patients with all grades of heart failure The Panel did not consider that the statement that the possible benefits of Amias in this patient group was currently under investigation negated the overall positive impression given. The Panel noted that under special warnings and special precautions for use, the Amias SPC stated that in patients with severe heart failure particular adverse events, although a possibility with AIIRAs, had not been reported with Amias. Even though these events had not been reported with Amias, the Panel did not consider that the statement in the information pack that candesartan would be well tolerated in patients with CHF and concomitant hypertension accurately reflected the warning/precaution given in the SPC with regard to severe heart failure. The statement was misleading and a breach of Clause 7.2 was ruled. The Panel considered that the alleged breach of Clause 3.2 was covered in its ruling in point 1a above.

c References to "well tolerated"

COMPLAINT

Bristol-Myers Squibb and Sanofi stated that this section

purported to present data on candesartan in the treatment of CHF and stated that the medicine was well tolerated in CHF, but had not included the most up-to-date evidence. Of particular concern was the fact that it did not include any information about the RESOLVD trial, which was the largest heart failure study conducted with candesartan (n = 769). The RESOLVD study was stopped prematurely due to an increased mortality rate in the patient groups that received either candesartan or candesartan and an ACE inhibitor. Bristol-Myers Squibb and Sanofi stated that this information was known at the time of preparation of the information pack. A breach of Clause 7.2 of the Code was alleged.

Bristol-Myers Squibb and Sanofi pointed out that although Astra and Takeda had agreed with their view on the heart failure data, and had agreed to alter the information pack, they had not agreed to stop using the information pack whilst the new brochure was prepared.

RESPONSE

Astra and Takeda stated that the information pack summarised the published data available at the time of preparation of the document. In December 1997 the RESOLVD trial had been presented but the results were not published in the abstract available at the American Heart Association 1997 meeting. Results of the initial analysis given at an oral presentation at the AHA meeting were quoted in Scrip, but these results were not published in a scientific journal at the time. At the time of presentation there were comments from leading cardiologists advising caution in reading too much into the results of this study as the data was from such small numbers of patients. Therefore this unpublished study was not included.

The RESOLVD trial was designed to examine the effects of Amias on left ventricular function, exercise capacity, neurohormones and tolerability. It was not powered to show an effect on clinical events or death. The study was stopped at an interim stage, as there was a trend towards fewer clinical events (mostly hospitalisation due to heart failure) in the group treated with enalapril alone However, the final analysis of RESOLVD showed no significant difference between Amias and enalapril on ventricular function, quality of life or in any clinical events, including mortality. Both Amias and enalapril were well tolerated. The RESOLVD advisory committee stated that there was no clear evidence of harm from use of Amias in heart failure when compared with enalapril

Astra and Takeda submitted that the section of the information pack in question was entirely consistent with the findings of the RESOLVD study. The Scrip article referred to by the complainants correctly highlighted that there was some debate between the advisory committee of the study and its lead investigator about the decision to stop the trial and that once all patients were included in the analysis, there were no significant differences between the Amias and enalapril treated groups.

Astra and Takeda stated that in December 1997, the final analysis of the RESOLVD data had not been completed or published in a scientific journal. However, as there was now new published information available from the RESOLVD trial, it had reviewed and updated the information pack; this was completed in July 1998.

PANEL RULING

The Panel considered that its ruling in point 1a above that too much information had been given on the use of Amias in heart failure and the section amounted to the promotion of an unlicensed indication in breach of Clause 3.2 of the Code was relevant to the allegation it was now considering.

The Panel noted that the information pack had been prepared in December 1997. Clause 7.2 required that information, claims and comparisons be fair, balanced and based upon an up-to-date evaluation of all the evidence. The Panel noted that if new evidence became available promotional items might have to be changed to reflect that evidence.

The Panel noted that mortality data from the RESOLVD trial had been presented orally at the American Heart Association Meeting and subsequently published in Scrip, 18 November 1997, in an article headed "Candesartan mortality concerns stop trial". The trial compared the effect of candesartan, enalapril and a combination of the two in heart failure patients. Primary endpoints were ventricular function, exercise capacity, effect on neurohormones and quality of life. The trial was not powered to show an effect on clinical events or death. After the trial had been halted an analysis of the data showed that death rates and hospitalization in patients receiving candesartan, either as monotherapy or in combination with an ACE inhibitor, was higher than in the other group but that the differences between the three patient groups was not statistically significant.

The Panel noted the response from Astra and Takeda. It noted that the RESOLVD study was neither aimed nor powered to detect an effect on clinical events or death. The Panel therefore considered that it was reasonable not to refer to the morality data from RESOLVD and ruled no breach of Clause 7.2 of the Code with regard to the information pack as generated in December 1997. The situation had been kept under review by the companies and following new information about the RESOLVD trial the information pack had been amended.

2 Amias Detail Aid

a Claim "Am I as .....outstanding in the treatment of hypertension?"

This claim appeared on the front cover of the detail aid.

COMPLAINT

Bristol-Myers Squibb and Sanofi stated that they were informed by Astra and Takeda that there was a previous Code of Practice Panel ruling of no breach of the Code with regard to a journal advertisement, which also included a similar wordplay of "Am I as.....outstanding in the treatment of hypertension?". However, in the journal advertisement at issue in the previous complaint, the question was followed by the answer "You decide" which meant that the reader could decide for themselves. The detail aid was different.

Bristol-Myers Squibb and Sanofi alleged that the question

together with the visual imagery used was in breach of Clause 7.8 of the Code.

Despite the questioning format, the wordplay 'Am I as.....?' (ie "Amias") juxtaposed with the word 'outstanding' was designed to lead the reader to believe that candesartan was, in some way, outstanding. The definition of "outstanding" was "eminent", "conspicuous" because of "excellence" or "remarkable in a specified field". The term was one that therefore indicated superiority.

The question was posed as a rhetorical one and was left unanswered. There was no option for the reader to think that he/she could decide for themselves whether or not candesartan was outstanding. Instead, it implied that candesartan (ie "Amias") was outstanding. This therefore constituted an exaggerated claim about candesartan.

However, there was no data to support the view that candesartan was outstanding either in the treatment of hypertension or compared to other marketed AIIRAs. For example candesartan was not the only AIIRA to demonstrate that it had a tolerability profile comparable to placebo across the dose range. It was not the only AIIRA to demonstrate non-competitive insurmountable binding to the AII receptor resulting in a long duration of action. It was not the only AIIRA that had a clear dose response in efficacy with no plateauing of effect within the licensed dose range.

Furthermore this rhetorical question appeared on the front page of the promotional brochure next to a picture of a tall building surrounded by shorter buildings. This visual imagery implied that candesartan, like the tall building, stood out above all others.

Bristol-Myers Squibb and Sanofi were also particularly concerned that this theme of exaggerated claims was continued in the latest promotional campaign (see point 3 below).

RESPONSE

Astra and Takeda stated that a detail aid was designed to be used as a focus for discussions between representatives and doctors; the item was not left with doctors and they did not read it alone. It was implicit in the nature of the item and the way the data was presented that doctors would decide what they thought of the product by discussing the information shown with the representative. The sentence 'Am I as.....outstanding....' was presented as a question, not a statement. To state that the readers of the detail aid would not be able to decide for themselves did not recognise their intelligence.

Astra and Takeda believed that Amias had features which clearly differentiated it. The dictionary definition of "outstanding" was "conspicuous or eminent, because of excellence or remarkable in a specified field" (Oxford Encyclopaedic English Dictionary). Astra submitted that Amias stood out from other antihypertensive agents for the following reasons:

– Amias was an AIIRA. This class stood out from all other current classes of antihypertensive agents in that its members had a tolerability profile comparable to placebo across the dose range in clinical trials. They had not claimed that Amias was the only AIIRA to do this.

– Amias had been shown to demonstrate a high degree of insurmountable binding to the AII receptor. The slow dissociation of Amias from the AII receptor had been suggested to be correlated to a long-sustained duration of action. The degree of insurmountability was the highest of all the AIIRAs.

– Amias had a high trough peak ratio, the highest range reported in the class of AII antagonists.

– Amias demonstrated a clear dose response in efficacy with no evidence of plateauing of effect within the licensed dose range in contrast to the older members of the AIIRA class. Astra did not claim that Amias was the only AIIRA to do this.

– Amias stood out from the other AII antagonists in terms of price.

Astra and Takeda pointed out that all of these points were presented in Cases AUTH/666/1/98 and AUTH/667/1/98, where the Panel had ruled no breach of the Code.

Astra and Takeda did not believe that the statement was exaggerated, nor that the omission of the answer 'You decide' made the detail aid different to the previous journal advertisement which was not ruled in breach of the Code.

PANEL RULING

The Panel noted that the previous cases (AUTH/666/1/98 and AUTH/667/1/98) concerned a journal advertisement containing the phrase "Am I as ....outstanding?" which was adjacent to an illustration showing the architectural features at the top of a skyscraper. It was alleged that the phrase in question implied that the product had some special merit in breach of Clause 7.8 of the Code. Beneath the phrase the advertisement discussed product features and concluded "The real test though is to prescribe Amias. Then ask yourself if it stands out from the alternatives." The Panel noted that the advertisement had not made the specific claim that Amias was outstanding. It was for the reader to decide whether the features of Amias detailed set it apart from alternative treatments. On balance the Panel had ruled no breach of the Code.

The Panel turned to the present case. The front page of the detail aid contained an identical illustration of the building adjacent to the phrase "Am I as .....outstanding in the treatment of hypertension?" The Panel considered that this page was different to the journal advertisement. There was no discussion of the clinical features of Amias.

The Panel noted that each page of the detail aid used plays on the word Amias. The answer to the question on the front page was not addressed by the content of the detail aid. The Panel considered that the front page of the detail aid implied that Amias was outstanding in the treatment of hypertension and this was exaggerated. The Panel ruled a breach of Clause 7.8 of the Code.

b Claim "Am I a Smooth acting anti-hypertensive?'

The claim appeared as the heading to page 5 of the detail aid which referred to trough-to-peak (T:P) ratios. The page was sub-headed "A high trough-to-peak ratio

indicates consistent 24 hour effect" and in similarly large type further down the page was the claim "Amias has a high trough-to-peak ratio". Beneath this claim was a histogram entitled "Range of trough-to-peak ratios at once daily dosing (placebo adjusted) as measured in various studies (DBP)". The histogram showed the T:P ranges for Amias 8-16mg (80-100), Iosartan 50-100mg (60-87%), irbesartan 150mg (60-70%) and valsartan 80mg (66%). The AIIRAs were placed in descending order of magnitude with reference to their T:P ratios.

COMPLAINT

Bristol-Myers Squibb and Sanofi stated that this page presented the trough-to-peak (T:P) ratios of four angiotensin II receptor antagonists as a histogram, joined on a continuous line at the x-axis as if the data were derived from a single study. The histogram as presented was misleading and unfair.

The T:P ratio of candesartan had not been compared to the other three AIIRAs in a single comparative trial. The data points for the comparison were obtained from four different studies. It was not valid to compare the T:P ratios derived from different studies in this way. The data was presented in this way to imply a special merit of candesartan. Equivalent doses of the AIIRA s had not been established. The histogram did not therefore, compare trough:peak ratios at equivalent antihypertensive doses. The graph implied that a T:P ratio of 80-100% was clinically superior to that of 60-70%. This was misleading as the clinical significance of a T:P ratio of more than 50% was not known.

Breaches of Clauses 7.2 and 7.6 were alleged.

RESPONSE

Astra and Takeda submitted that the histogram was not misleading.

T:P ratio was a well recognised measure of how well the antihypertensive effect was sustained over the dose interval and was usually expressed as a percentage. Guidelines had recommended a T:P ratio of more than 50% for once daily dosing (Lipicky 1994).

It would not be reasonable to expect one study to compare all four treatments. The chart was quite clearly labelled from different studies. This was clarified further by the individual referencing for each study. The histogram compared T:P ratios as given in the product SPC or product monograph (where available) or, if not available, from published studies. As Bristol Myers Squibb and Sanofi had pointed out, equivalent doses of the AIIRAs had not been established and it was therefore not possible to compare T:P ratios at equivalent antihypertensive doses. As far as possible, the doses given covered the normal maintenance dose range for each product. The page in the detail aid was the right hand page of a double page spread which aimed to show the relationship between T:P ratio and consistent 24 hour control of blood pressure. The chart made no claim of clinical superiority over the other agents, but simply stated the quoted T:P ratios of the available AII antagonists.

Astra and Takeda submitted that the AII antagonists were a relatively new class of antihypertensive agent and all of these had a once daily dose interval. The T:P ratio was an acknowledged indicator of consistency of antihypertensive effect and was a relevant feature to discuss. No claim was made regarding the clinical significance of the various T:P ratios currently available for the AII antagonists and, where possible, comparative data had been used as in the case of losartan and Amias.

PANEL RULING

The Panel considered that great care ought to be taken when making comparative claims based on the results of different studies. The Panel noted that no basis for the selection of the various studies had been given. The Panel noted the submission that the doses of each medicine given had, as far as possible, covered the normal maintenance dose range for each product. The doses for Amias and Iosartan covered the normal dose range (8-16mg and 50-100mg respectively) but only the lowest doses for irbesartan and valsartan had been given (150mg and 80mg respectively)

The Panel noted that the T:P ratios depicted in the histogram ranged from 80-100% for Amias to 55% for Valsartan. The paper by Lipicky (1994) stated that in general a T:P ratio of 50-75% indicated that blood pressure would be controlled throughout the dosage interval. The Panel noted that the paper also stated that T:P ratios, although valuable parameters, were a primitive means of estimating the appropriateness of a dose interval and that there were problems associated with their characterisation and interpretation.

The Panel noted that Astra and Takeda had agreed with the complainants that therapeutically equivalent doses of AII antagonists had not been established. Although guidelines had recommended a T:P ratio of over 50% for once daily dosing the Panel noted the complainants view that the clinical significance of a T:P ratio of over 50% was not known.

In the opinion of the Panel the histogram together with the claim "High trough-to-peak ratio indicates consistent 24 hour effect" created the impression the T:P ratios based on the stated doses were directly comparable and that Amias with a T:P of 80 - 100% would be a smoother acting antihypertensive than the other AIIRAs depicted and this was misleading. The Panel ruled a breach of Clause 7.2 of the Code. The Panel also ruled a breach of Clause 7.6 of the Code as the impression from the histogram was that the data was from a comparative study and this was not so.

3 Amias Journal Advertisement

The double page advertisement featured the world cup football trophy between the phrases "Am I as...." and "desirable?" The text was headed "Amias vs Hypertension" and the subsequent text discussed, in a number of points, various clinical features of Amias. The fourth point was entitled 'Crowd pleaser' and stated that "Amias is suitable for a wide range of hypertensive patients". The concluding paragraph stated "So, when you are looking for a winning treatment for your patients with hypertension, why not award them the desirable benefits of Amias?"

a Claim "Am I as ..... desirable?"

COMPLAINT

Bristol-Myers Squibb and Sanofi alleged that the rhetorical question "Am I as.... [ie Amias] desirable?" was used in order to create the impression that candesartan therapy was more desirable than other antihypertensive therapy.

The question was placed beside a picture of the world cup football trophy being held aloft to imply that candesartan had superiority - the implication was that it had competed and come out as the winner. This was an exaggerated claim which could not be substantiated by data. A breach of Clause 7.8 of the Code was alleged.

RESPONSE

Astra and Takeda stated that this world cup advertisement had appeared in several journals (including GP, Hospital Doctor and MIMS) throughout the time of the world cup football competition.

The visual used did not imply that Amias had been declared the winner. As the strapline clearly indicated the world cup football trophy was used as a highly topical symbol of aspiration or desire and something to strive for. The text clearly stated that the competition was "Amias vs Hypertension" and referred to those qualities which made the use of Amias suitable for patients with hypertension; no claims were made versus any other antihypertensive agent. The section concluded by asking whether Amias had desirable benefits in hypertension and there was no suggestion of superiority over other agents.

PANEL RULING

The Panel considered that the world cup trophy was presented in the advertisement as a standard to achieve. The accompanying question asked readers to consider whether the clinical features discussed in the advertisement measured up to that standard. The advertisement referred to the search for a winning treatment but did not state or imply that Amias was the winning treatment. The Panel noted that the strapline beneath the product logo was "Angiotensin II antagonism - towards the ultimate".

The Panel did not accept that the use of the world cup football trophy in this context constituted an exaggerated claim and ruled no breach of Clause 7.8 of the Code.

b Claim "Crowd pleaser"

"So, when you are looking for a winning treatment for your patients with hypertension, why not award them the desirable benefits of Amias?"

COMPLAINT

In the last paragraph a claim made under the heading "Crowd pleaser" read as above. Although this was phrased as a question, it was inferring that the reader should try the winner which was candesartan. More importantly, the winner had been equated to the world cup football team which was really the best of the best. Bristol-Myers Squibb and Sanofi alleged that this claim implied special merit which could not be substantiated.

RESPONSE

Astra and Takeda stated that the claim concluded the section of copy under the heading "Amias v Hypertension" and it was perfectly clear that the statement related to winning (ie success) against hypertension. Doctors were looking for a treatment that would help them win against hypertension and the statement suggested that they should consider using Amias. It did not attempt to imply that Amias was the winner or the best of the best and it could not be interpreted as doing so. To assert that it did was to deliberately misconstrue the meaning.

Astra and Takeda pointed out that this advertisement was no longer in use after the completion of the World Cup tournament 1998.

PANEL RULING

The Panel noted its comments in point 3a above. It noted that the statement in question appeared beneath the heading "Crowd pleaser", beneath the points discussing the clinical features of Amias.

In the opinion of the Panel the statement in question did not claim or infer that Amias was the winning treatment, merely a winning treatment for hypertension. The Panel ruled no breach of Clause 7.8 of the Code.

Complaint received **5 August 1998**

Cases completed **19 October 1998**

CASE AUTH/754/8/98

DIRECTOR v HOECHST MARION ROUSSEL

Nurse facilitated audit

This case arose from the Panel's consideration of a previous case, AUTH/712/5/98, which concerned a nurse advisor made available to a general practice by Hoechst Marion Roussel. The Panel had been concerned about the role of such nurses in the assessment of patients for therapeutic substitution from their current ACE inhibitor therapy to Hoechst Marion Roussel's product Tritace (ramipril). It seemed to the Panel that there was little difference in principle to the situation in a recent case, AUTH/689/3/98, in which a company had been ruled in breach for providing finance to a health authority so that the health authority could reimburse costs incurred by practices when considering switching patients from a competitor's product to that of the sponsor company.

The Panel noted that there were differences between the previous case and the one now before it. There was no agreed figure for the number of patients to be switched in the present case and no payment was made to the practice. Doctors were not obliged to switch patients but the submission from Hoechst Marion Roussel made clear that the switch related to using its product. In the Panel's view, the provision of the service was too closely linked to the promotion of Tritace for it to be considered to be a medical or educational good or service The effect of the audit would be to increase the prescribing of Tritace at the expense of other ACE inhibitors.

The Panel noted that the provision of the audit was not dependent on the prescription of Tritace but nonetheless considered that the service amounted to an inducement to prescribe it. A breach of the Code was ruled.

Upon appeal by Hoechst Marion Roussel, the Appeal Board expressed particular concerns regarding the role of the nurse provided to facilitate the audit. In addition to general training the nurse received specific product training on Tritace. The nurse was to carry out an audit of patient records and make a recommendation as to the viability of a switch for each patient. Then, while running the clinic, the nurse would tell patients about ramipril if requested to do so by the doctor. In the Appeal Board's view the nurse was clearly associated with Tritace.

In the Appeal Board's view the provision of the audit service and the arrangements for the audit were too closely linked to the promotion of Tritace for it to be considered a medical and educational good or service. The promotion of medical and educational goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine. Overall, the Appeal Board considered that in these particular circumstances the service, as provided by Hoechst Marion Roussel, amounted to an inducement to prescribe Tritace and upheld the Panel's ruling of a breach of the Code.

COMPLAINT

During its consideration of Case AUTH/712/5/98, the Panel became concerned as to whether Hoechst Marion Roussel Limited's involvement in the assessment of patients for therapeutic substitution from current ACE inhibitor therapy to its product Tritace (ramipril) and the post-switch audit were legitimate activities. It seemed to the Panel that there was little difference in principle to the situation in a recent case (AUTH/689/3/98) in which a company had been ruled in breach of Clause 18.1 of the Code for providing finance to a health authority so that the health authority could reimburse costs incurred by practices when considering switching patients from a competitor's product to that of the donor company. The Panel decided that this matter should be taken up with Hoechst Marion Roussel under the provisions of Paragraph 16 of the Constitution and Procedure in relation to a possible breach of Clause 18.1 of the Code.

RESPONSE

Hoechst Marion Roussel outlined the promotional strategy for its product Tritace in the context of the concern raised by the Authority. Following publication of the NHSE's Executive letter (95) 8 Annex B, which asked general practitioners to consider switching to therapeutically equivalent drugs wherever clinically appropriate, the company recognised the potential for general practitioners to make cost savings in relation to their prescribing of ACE inhibitors. Hoechst Marion Roussel's product, Tritace, was competitively priced in relation to others in the class and its proposition to a number of surgeries had been that by switching appropriate patients to ramipril from other ACE inhibitors, savings on the practice drugs bill might be made without compromising high standards of patient care, thus freeing funds which might be utilised to the benefit of patients.

Hoechst Marion Roussel further recognised that for any individual practice there would be a considerable workload and a high level of commitment required to achieve a well managed therapeutic substitution. The company had, therefore, appointed an experienced team of representatives, known as healthcare development managers (HDMs), one of whose roles it was to firstly discuss with practices the concept of therapeutic substitution and, if those practices decided to undertake such a process in connection with ramipril, to facilitate its initiation, monitoring and review. Hoechst Marion Roussel emphasised that the service was provided without obligation on the practice to actually undertake a therapeutic substitution. Its purpose was to facilitate audit and the identification of patients who might be considered appropriate for switching. The decision regarding which patients to switch and how many, was entirely the responsibility of the doctor concerned.

Clearly it would be inappropriate for Hoechst Marion Roussel's representatives to have any clinical involvement in any of this process or to have access to any patient-specific information. The HDMs were therefore empowered, if so requested by the doctors involved, to brief an agency retained by Hoechst Marion Roussel to supply appropriately trained and qualified independent personnel, to provide either a nurse advisor or IT

specialist to attend the surgery in question to undertake parts of the therapeutic substitution process as directed by the doctors concerned. The therapeutic substitution was directed only at patients with mild to moderate hypertension who were adequately controlled on other ACE inhibitor therapy.

Hoechst Marion Roussel provided details of the process:

1 In the course of normal promotional activity the GP representative would highlight the cost benefits of Tritace compared to other once a day ACE inhibitors for the treatment of mild to moderate hypertension. If the GP showed interest the representative would ask three questions:

- Was the practice looking at ways of managing costs in its prescribing budget?
- Had the practice undertaken any cost savings measures such as therapeutic substitution?
- Was the practice interested in meeting an HDM to discuss this subject?

At this point the representative would offer to arrange for an HDM to visit the practice and initially meet with the senior partner and the practice manager.

2 The practice would be contacted by an HDM to arrange an appointment to further discuss therapeutic substitution.

The HDMs were the coordinators of the therapeutic substitution in so far as it concerned the company and as such were the people who had direct responsibility for ensuring that the correct level of service was offered to the practice to assist it in its consideration of substitution.

3 The HDM would initially meet with the senior partner and the practice manager to discuss the concept of therapeutic substitution. If they agreed to the concept, then a further meeting would be arranged inviting all the GPs and other appropriate members of the practice to a presentation by the HDM on the potential cost savings of switching patients from other ACE inhibitors to ramipril.

4 The agency service was explained by the HDM (IT specialist support to audit and screen patients via computer, nurse advisors to run hypertension clinics pre- and post-switch). This service was offered at no charge to the practice. All payment for the service was made by Hoechst Marion Roussel directly to the agency, no payment was made directly to the practice. The service was provided with no obligation for the practice to switch patients to ramipril. The service merely assisted the doctor to identify potential patients; the decision actually to change the prescription was made solely by the practice.

5 In the discussions with the practice clear objectives and a list of key contacts for the agency personnel were identified. A protocol agreement form, which authorised Hoechst Marion Roussel and agency activities, was signed by the lead GP. Once the protocol was agreed the HDM would progress the booking of agency activities.

6 Based on the patients identified by the GP and contacted by the surgery, the agency nurse would run the clinic, offer a phlebotomy service and other health checks and be able to explain the role of ramipril to patients as agreed with the responsible GP.

7 The facility for a follow up clinic was offered.

8 The practice was revisited in 3 months by the HDM to evaluate and feedback.

On the following basis Hoechst Marion Roussel did not believe that the activity described was in breach of Clause 18.1 of the Code:

1 Discussions with HDMs on therapeutic substitution were initiated because of interest expressed by the practice concerned.

2 The hypertension audit service was provided as a service to the practice with no obligation to prescribe. Hoechst Marion Roussel believed that this came within the definition of educational goods and services according to Clause 18.1 of the Code.

3 The therapeutic substitution process was directed only at patients with mild to moderate hypertension who were adequately controlled on other ACE inhibitor therapy.

4 Activities undertaken by Hoechst Marion Roussel in respect of the Tritace auditing and switch process differed materially from those quoted in Case AUTH/689/3/98 - financial support for audit, in that:

- It was not a condition of the audit and follow up service that patients were actually switched to ramipril.
- The practice itself was not reimbursed directly in any way. The services were provided by an independent third party.

In support of the above, Hoechst Marion Roussel provided a copy of its contract with the agency (which included payment details), an example of a booking form for the service, the HDM briefing document and the roles and responsibility documents.

PANEL RULING

The Panel noted that pharmaceutical companies were becoming increasingly involved in facilitating practice audits and providing specialist nurses to general practices. Such activities were not necessarily unacceptable. Pharmaceutical companies should, however, ensure that the arrangements for the provision of such services complied with all the relevant requirements of the Code, in particular Clause 18.1. The impression created by the arrangements should be borne in mind. The Panel noted that a working party, established by the ABPI Board of Management, was preparing further guidance on the provision of medical and educational goods and services.

The Panel noted the supplementary information to Clause 18.1 that the provision of medical and educational goods and services must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine.

The Panel examined the report for Case AUTH/689/3/98 where a company had been ruled in breach of the Code for providing grants to a health authority to pay costs incurred by general practitioners in reviewing their patients and deciding which to switch from a competitor's product to that of the sponsor. The reimbursement payment was triggered by a switch in at least 80% of patients identified. The Panel considered that

the purpose, and certainly the effect, of the sponsorship was to boost the prescribing of the sponsor's product at the expense of that of the competitor. Funding for this purpose was unacceptable.

The Panel noted that there were differences between the previous case and the one now before it. There was no agreed figure for the number of patients to be switched in the present case and no payment had been made to practices.

The Panel examined the NHS Executive letter EL/(95)8 provided by Hoechst Marion Roussel. One of the regional objectives, given in Annex B, was to identify the scope for further efficiency improvements through more cost effective prescribing and by considering areas identified by the Audit Commission in its report "A Prescription for Improvement". One of these was stated in the letter to be switching to cheaper therapeutically equivalent drugs wherever clinically appropriate.

The Panel noted Hoechst Marion Roussel's submission that the arrangements for the therapeutic switch were such that the service was provided without obligation on the practice to actually undertake a therapeutic substitution. Its purpose was to facilitate audit and identification of patients who might be considered appropriate for switching. The decision regarding which patients to switch and how many was the responsibility of the doctor concerned. The Panel noted that after preliminary discussion between the representative and a doctor, the representative would arrange for the HDM who would initially meet with the senior partner and the practice manager to discuss the concept of therapeutic substitution. If they agreed to the concept then a further meeting would be arranged inviting all GPs in the practice and other staff to a presentation by the HDM on the potential cost savings of switching patients from other ACE inhibitors to ramipril.

The Panel noted that the nurse running the pre switch clinic would offer a phlebotomy service and other health checks as well as explaining the role of ramipril to patients.

The Panel considered that this was a difficult case. Patients with mild to moderate hypertension who were adequately controlled on ACE inhibitor therapy were being switched to Tritace as a result of an audit established and paid for by the manufacturers of Tritace, Hoechst Marion Roussel. The Panel noted that the Executive letter referred to switching to cheaper therapeutically equivalent medicines wherever clinically appropriate and questioned whether it was clinically appropriate to switch patients already adequately controlled on ACE inhibitor therapy to Tritace. The Panel considered it was a possibility that during the switch process the blood pressure of some patients might fluctuate until they were stabilised on Tritace.

The Panel noted that doctors were not obliged to switch patients but the submission from Hoechst Marion Roussel made clear that the switch related to using its product ramipril. In the Panel's view the provision of the service was too closely linked to the promotion of Tritace for it to be considered to be a medical or educational good or service. The effect of the audit would be to increase the prescribing of Tritace at the expense of other ACE inhibitors.

The Panel noted that the provision of the audit was not dependent on the prescription of Tritace but nonetheless considered that the service amounted to an inducement to prescribe Tritace. A breach of Clause 18.1 of the Code was ruled.

APPEAL BY HOECHST MARION ROUSSEL

Hoechst Marion Roussel stated that its appeal was made in the common understanding of the following:

1 This case was brought under Paragraph 16 of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority following the ruling in Case AUTH/712/5/98.

2 The Panel had drawn the company's attention to three rulings (and two appeals) in previous similar, but not identical, cases: AUTH/517/3/97, AUTH/550/5/97 and AUTH/689/3/98.

3 The ABPI Board of Management had established a working party which had prepared further guidance on the provision of medical and educational goods and services. The report had not yet been approved by the ABPI Board and thus it had not yet been put into the public domain. Hoechst Marion Roussel was not aware of its contents at the time of this appeal.

4 The details of the Hoechst Marion Roussel nurse facilitated audit service were familiar to the Authority, having been presented, clarified and considered in connection with both this case and the previous one (Case AUTH/712/5/98)

5 The Panel had considered that this was a difficult case to rule on.

Hoechst Marion Roussel stated that the grounds for its appeal against the Panel's ruling, of a breach of Clause 18.1 of the Code, were:

a) The nurse facilitated audit service was established as a legitimate activity as part of the promotional campaign for Tritace; it adhered to the letter and spirit of the Code in respect of promotion;

b) Such schemes were widespread, encouraged by healthcare professionals and the NHS, and were accepted (state-of-the-art) activities which permitted companies to respond to the changing market-place and trading relationships;

c) An audit service, linked to a company, therapy or product, did not in itself constitute an inducement to prescribe;

d) The service did not contain within it any inducement to prescribe. All prescribing decisions were those of the doctor, made freely and uncompromised by the provision of, continuation of or payment for the audit service.

Hoechst Marion Roussel noted that Clause 18.1 of the Code as written related to the inducement by personal financial gain or benefit in kind of a potential prescriber. In so doing it reflected very much the professional code of the General Medical Council in setting down the proper ethical and professional behaviour of any medical practitioner in relation to a representative of the pharmaceutical industry.

At all times the doctor must feel and be free to prescribe

the appropriate medication of his/her choice for the appropriate patient, and must not be coerced either overtly or covertly by activities of the manufacturer. The doctor was thereby able to act in the best interests of the patient.

Promotional activity by the pharmaceutical industry must thus be seen as such in order that the doctor could make up his/her own mind in relation to the context in which product information was offered. Promotional activity must not be disguised.

Hoechst Marion Roussel stated that in providing supplementary information to Clause 18.1 the Authority had extended the term 'inducement' beyond that of personal gain, which would amount to corrupt behaviour and was totally against the doctor's professional code, to relate to those activities in which inducement/coercion might be regarded as secondary to a non-personal gain, which might include goods and services which otherwise brought benefit to the NHS, to the practice or to the patient, for example through activities which enhanced the quality or standard of diagnosis or patient management/treatment.

Hoechst Marion Roussel submitted that there was a large qualitative difference between inducement of the doctor through personal gain and secondary to non-personal gain or advantage (the gain was to the NHS, practice, patient or charity). Such differences were not elaborated in the Code, but must have a bearing on judgements made in determining cases where inducements were alleged to have taken place.

Nevertheless, Hoechst Marion Roussel agreed entirely with the principle that in prescribing medicines, all forms of inducement were unacceptable, since they compromised the professional ethics of the doctor to make free prescribing decisions.

It was a basis of this appeal that the audit service did not in any sense described above or by the Code involve inducement of the doctor to prescribe ramipril. Prescribing decisions were entirely the responsibility of the doctor, who was aware of this at all times, and the provision of the audit service was not dependent on either the decision to switch to ramipril and prescribe the drug or on any pre-defined quantum of prescribing.

Whilst Hoechst Marion Roussel did not wish to comment on the other cases brought to its attention by the Authority, it did seem to the company that a critical difference between those and the present case rested on the above point. In previous cases linkage could be shown between prescribing decisions and the provision or continuation of the good or service. In the case in question no such linkage existed. Indeed in establishing the service great care was taken to ensure that no such linkage was possible in view of the very implications that such an inducement would bring.

Hoechst Marion Roussel noted that the Panel acknowledged "that the provision of the audit was not dependent on the prescription of Tritace but nonetheless considered that the service amounted to an inducement to prescribe Tritace".

Hoechst Marion Roussel considered that the Panel's ruling was unsound on this point and that this was the major ground for the appeal. It was of critical importance that there was no linkage between the audit and the prescription of the medicine, since this would be the basis for an inducement to prescribe which would make the scheme unacceptable.

Hoechst Marion Roussel stated that since the audit formed part of the promotional campaign for Tritace, and must in itself be considered as promotion (see below), it was not surprising that in part there was close association between it and the product. However this did not in itself amount to an inducement to prescribe, although it might explain the Panel's difficulty in seeing total separation between the audit service and the product. In its promotion the company had been open about the comparative properties of Tritace, including cost-effectiveness, and about its motives to offer the audit service to the NHS.

The decision to avail his/her practice of the audit service was that of the doctor, encouraged perhaps by the fact that it was provided at no cost to the practice. Nevertheless, all prescribing decisions associated with a review of the practice management of hypertension were those of the clinicians, made openly and independently of any other influence.

Hoechst Marion Roussel noted that the Panel recognised that the provision of medical and educational goods and services by the pharmaceutical industry was widespread, growing and not discouraged by the NHS itself. This was particularly true in the present era of cost-consciousness, budgetary pressure and the general realisation that all the medical services which contributed to the high standards of medical management and treatment demanded by the healthcare professions and the public alike could not be provided out of current government funding. Some goods and services provided by the pharmaceutical industry and agreed with the NHS were today even dignified by the well-recognised, if somewhat nebulous, term of 'disease management programmes'.

Hoechst Marion Roussel noted that the Panel considered that such activities might still be appropriate, as long as there was no dependent link between them and the prescription, provision or sale of a medicine. The company agreed with this principle, whereas the Panel's ruling in this case seemed to be at odds with it. Whilst there was no evidence of a dependent link between the service and a switch prescription for ramipril (ie an inducement), the Panel had considered that an association between the service and the company's other promotional activity for the product, which the company acknowledged, might in itself constitute an inducement to prescribe.

Hoechst Marion Roussel stated that the consequence of the Panel's ruling, if upheld, would be to put out of bounds many or most of the industry's medical and educational goods and services because of their association with a company's products and the possibility that this juxtaposition in itself amounted to an inducement to prescribe. The company considered that such a draconian consequence would be impossible to enforce, would do great damage to the already fragile relationship between the industry and its customers, and would be a further affront to fair trading for those companies ruled against specifically. The company had great difficulty in either understanding or accepting the ruling in this case since it flew in the face of so many of

the accepted everyday transactions between the pharmaceutical industry and its 'customers', and threatened to undermine fair trading practices in a competitive marketplace.

Hoechst Marion Roussel stated that the common understanding of the provision of goods and services was that they were not unrelated to the motivation by companies to promote products and the provision of such goods and services in themselves must be considered promotional, and thus avoid the charge of unacceptable covert promotion.

In the absence of detailed guidelines in these matters, companies turned to the common understanding of accepted and acceptable practices (the state-of-the-art) as outline in documents already in the public domain. In the Textbook of Pharmaceutical Medicine, written particularly as a reference source for pharmaceutical physicians, whose job it was to make judgements on matters relating to the acceptability of promotion and advise their companies accordingly, it was written:

> "The provision of services to doctors and even directly to patients are an accepted form of promotion. Many responsible companies provide information and specific services which can be made available to patients by the treating physicians or nurses. Such services create a favourable impression of a company and its products in the minds of doctor, health professional or patient. For example, a videograph on the correct procedures for operating a nebuliser can be made available to patients through the doctor or the asthma nurse by the manufacturers of a nebuliser solution. This helps with branding or product preference by the doctor and patient. Similarly, funding practice nurses to be trained in the clinic management of asthma or 'hyperlipidaemia' helps to ensure that the patient is referred by the 'trained' nurse to the doctor for treatment. Because such items are provided by companies wishing to promote the use of their products they are classed as promotional activity. The Code of Practice and Medicines Act prohibit the advertising of prescription medicines to the public, i.e. patients and therefore services provided in this manner which bring companies into contact with patients must not constitute advertising for such product."

Hoechst Marion Roussel stated that pharmaceutical companies existed to discover, develop, manufacture and sell medicinal products. Whilst achieving success and acknowledgement of high ethical, technical and professional standards, pharmaceutical companies were neither altruistic nor charitable bodies.

The company had failed to think of any other company which offered a good or service to the NHS which was altruistic. Either directly or indirectly, they all served to enhance the image or reputation of the company, to establish its presence in a therapeutic area or to heighten awareness of and ultimately increase prescribing of its medicines. If the provision of goods and services was deemed in itself to be an inducement to prescribe, as seemed to be a consequence of the Panel's ruling in this case, then isolated rulings against individual companies threatened the principle of fair trading for those companies in the competitive marketplace. Hoechst Marion Roussel was concerned that if the Panel's ruling was upheld then ABPI member companies would be increasingly denied the opportunity to compete effectively in a changing and challenging healthcare environment, which demanded new approaches to meet new challenges (in this case addressing the issue of cost-effective prescribing of ACE inhibitors in hypertension). The company was concerned that the precedent set by the current ruling had a general applicability to all companies offering goods and services, including so-called 'disease management programmes'.

To refer more specifically to the case in question, Hoechst Marion Roussel submitted that it had acknowledged that the audit service was by common understanding a promotional activity related to the company's desire to increase sales of Tritace. This was neither denied or hidden. The motivation to encourage switching from one medicine to another ran through most individual promotional encounters between a pharmaceutical representative and prescriber and was deemed acceptable, indeed intrinsic, to the concept of promotion. In Tritace, Hoechst Marion Roussel had an ACE inhibitor which was not only recognised, through its product licences, to have the requisite efficacy, safety and quality for the class, but also which happened to be one of the most cost-effective ACE inhibitors available. It was for this reason, encouraged by the NHS Executive Letter EL(95)8 Annex B, that the nurse facilitated audit seemed an appropriate service to offer to practitioners to enhance the economic and clinical management of their hypertensive patients. The motivation to switch to Tritace came not from the availability of the service, however, but from the significant cost savings resulting from the change.

In Hoechst Marion Roussel's view, services such as audit and follow-up clinics were widely welcomed by health authorities and general practitioners, and indeed were activities which they were increasingly obliged to perform. Therefore the company's provision of such services clearly fulfilled a need, and was distinct from the act of prescribing Tritace, which was incidental to the process although coincident with it. Since the scheme fell within the term promotion, although not dependent on the prescription of the product, Hoechst Marion Roussel ensured that it adhered to the letter and spirit of the Code in respect of promotional items. Extensive safeguards and provisions to ensure that clinical and prescribing decisions could not be compromised and thus form an inducement to prescribe were built into the service:

a) The audit and follow-up clinics offered by the company were different to and separate from meetings in which the direct promotion of Tritace took place;

b) The audit process was conducted by an independent service not by company personnel.

c) Patient confidentiality was respected at all times; there was no access to patient information.

d) The provision of the scheme was not conditional upon any commitment at all to prescribe, administer or supply ramipril.

e) Payments for the provision of nurse services were made directly to the suppliers of those services.

f) No products were promoted to patients, although the nurse facilitator was trained to impart relevant and practical medical information about ramipril, after the prescribing decision had been made by the doctor, and if requested to do so by the doctor.

g) All prescribing decisions were made by the patient's doctor, including decisions to prescribe ramipril following review of the practice's prescribing of ACE inhibitors. The doctor was also responsible for determining the clinical appropriateness of a patient for switching from current treatment. The company certainly would not recommend any doctor to change the treatment of a patient controlled on anti-hypertensive therapy where a change in medication might put the patient at any risk or be deemed clinically inappropriate. Nevertheless Hoechst Marion Roussel was convinced that therapeutic substitution took place frequently in practice and was not believed to give rise to adverse consequences.

h) The clinic offered an enhanced clinical service to doctors separate from the considerations of therapeutic switching for cost-effectiveness reasons. It provided an historical audit on their case management, urea/electrolyte analysis giving information on renal function, information on disease progression and on potential for drug interactions, particularly in patients already on polypharmacy.

Hoechst Marion Roussel was also aware of the need to ensure the creation of a correct impression by the provision of medical and educational goods and services, whilst recognising that no guidelines currently existed. The company had tried very hard to put in place a system that would be regarded as ethically unimpeachable, and considered it had succeeded.

The company accepted, however, that lapses did occur in situations which were dependent on the correct interaction of people unfamiliar with each other's background, training, and position. The company noted that it had not appealed the Panel's ruling in Case AUTH/712/5/98 in relation to the conduct of a representative.

Hoechst Marion Roussel defended the company's decision to allow its representatives to open the discussion of the possibility of a nurse facilitated audit service. Many pharmaceutical companies employed their representatives in an administrative capacity in the implementation of such services. Representatives were the largest single group in any pharmaceutical company. To implement a service nationally to medicine without involving them would incur prohibitive costs. Without their involvement, the resultant loss of potential services would be detrimental to both patients and to the NHS.

APPEAL BOARD RULING

The Appeal Board considered that the provision of nurse facilitated audits by pharmaceutical companies was not necessarily unacceptable under the Code. The arrangements for the provision of such services needed to comply with the Code, in particular Clause 18.1. Each case had to be judged on its individual merits.

The Appeal Board noted that switching patients' medication represented a substantial commitment in terms of time and resources. There was no prohibition on promoting products on the basis of therapeutic substitution provided that the arrangements and materials complied with the Code.

The Appeal Board noted that the cost benefits of switching to Tritace were discussed with the practice prior to the audit. The audit service offered by Hoechst Marion Roussel was only implemented in those practices which had agreed to the concept of therapeutic substitution and decided to undertake such a process in connection with ramipril. The provision of the service was, therefore, linked to a practice's anticipated increased use of Tritace. There was, however, no actual obligation for the practice to switch any patients. The decision regarding which patients to switch and how many was the responsibility of the doctor.

The anticipated effect of the audit in question would, however, be to increase the prescribing of Tritace at the expense of other ACE inhibitors. The payment of the audit expenses by Hoechst Marion Roussel would benefit the practice by saving the practice the expense of carrying out the switch itself.

The Appeal Board expressed particular concerns regarding the role of the nurse provided to facilitate the audit. In addition to general training the nurse received specific product training on Tritace. The nurse was to carry out an audit of patient records and make a recommendation as to the viability of a switch for each patient. Then, while running the clinic, the nurse would tell patients about ramipril if requested to do so by the doctor. In the Appeal Board's view the nurse was clearly associated with Tritace.

In the Appeal Board's view the provision of the audit service and the arrangements for the audit were too closely linked to the promotion of Tritace for it to be considered a medical and educational good or service. The provision of medical and educational goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine. They must not bear the name of any medicine but might bear a corporate name.

Overall the Appeal Board considered that in these particular circumstances the service, as provided by Hoechst Marion Roussel, amounted to an inducement to prescribe Tritace and upheld the Panel's ruling of a breach of Clause 18.1.

The appeal was unsuccessful.

The Appeal Board noted that according to the documentation provided, an information technology specialist was also available to perform an audit of patient records on the practice computer. The Appeal Board was concerned that a non-healthcare professional might thus have access to patients' personal details. In the Appeal Board's view only healthcare professionals should have access to such data.

Proceedings commenced **16 July 1998**

Case completed **27 November 1998**

CASE AUTH/755/8/98

CONSULTANT MICROBIOLOGIST v THE LIPOSOME COMPANY

Promotion of Abelcet

A consultant microbiologist expressed concern that a representative from The Liposome Company was telling him to ignore the Abelcet (amphotericin B lipid complex) data sheet and use the product empirically at a lower than recommended dose. Following the representative's visit the complainant received, in addition to reprints of published papers and abstracts, a copy of an antibiotic protocol amendment in relation to guidelines issued by the haematology department of another hospital.

The Liposome Company submitted that while Abelcet was not licensed for empiric use it was the complainant who had initiated specific discussions with the representative regarding issues outside the licence.

The Panel noted that the accounts differed. The complainant stated that the representative promoted the empiric use of Abelcet at a dose of 2mg/kg/day. The representative stated that he had replied to questions asked of him by the complainant. The guidelines subsequently provided by the representative to the complainant referred to the empiric use of Abelcet 2mg/kg/day. (The licensed dose of Abelcet was 5mg/kg/day in known fungal infections.) Given the differing accounts the Panel was unable to determine precisely what had been said and ruled no breach of the Code in that regard.

The Panel noted that the representatives' briefing material included information on all of the modified amphotericin B products irrespective of whether it was within the terms of the marketing authorization. One section of the Abelcet training programme stated, under the heading "Clinical Indications", that "Abelcet may have a role in...the empiric treatment of suspected fungal infection, but this has not yet been established." There was no indication that this information was not to be used promotionally. The Panel acknowledged that representatives might well be asked questions about unlicensed uses of their company's medicines but considered that companies should give instructions which clearly differentiated between information that could be used promotionally and information which was for the representative's personal education. The Abelcet briefing material was inadequate in this regard and a breach of the Code was ruled.

COMPLAINT

A consultant microbiologist expressed concern about a visit from a representative of The Liposome Company who was promoting Abelcet (amphotericin B lipid complex) for use in intensive care and in febrile neutropenic patients. The complainant was concerned that the representative was telling him to ignore the data sheet and to use Abelcet empirically at a dose lower than that recommended in the data sheet.

Following the visit the complainant received some re-prints of published papers, abstracts and a copy of an antibiotic protocol amendment in relation to guidelines issued by the haematology department of another hospital.

The antibiotic protocol amendment stated that Abelcet should be substituted for AmBisome (NeXstar Pharmaceuticals Ltd's product) in patients receiving autologous marrow or autologous PBSC transplants, and in non-transplant patients.

The identity of the complainant had not been made known to The Liposome Company. This was in accordance with the complainant's wishes.

RESPONSE

The Liposome Company stated that the representative had passed, with distinction, the ABPI examination in 1993. During his term of employment with the company he had demonstrated exemplary standards of conduct. Neither his professionalism nor his ethical conduct had previously been questioned. He had been put in an invidious position because the identity of the complainant had not been provided and so he had to make assumptions about the alleged events.

The Liposome Company stated that the representative denied that he told the complainant to ignore the data sheet or that he encouraged the complainant to use the product for empiric usage at doses of 2mg/kg/day.

Abelcet was indicated for the treatment of severe invasive candidiasis. It was also indicated as second line therapy for the treatment for severe systemic fungal infections in patients who had not responded to conventional amphotericin B or other systemic antifungal agents, in those who had renal impairment or other contraindications to conventional amphotericin B, or in patients who had developed amphotericin B nephrotoxicity. Abelcet treatment was indicated as second line treatment for invasive aspergillosis, cryptococcal meningitis and disseminated cryptococcosis in HIV patients, fusariosis, coccidioidomycosis, zygomycosis and blastomycosis.

Promotion of Abelcet in the intensive care setting was permitted within the constraints of the marketing authorization and thus the representative was complying with the Code during these discussions. Likewise the treatment of febrile neutropenic patients was also permitted provided that the treating physician had diagnosed a fungal infection and, where the infection was not systemic candidiasis, conventional amphotericin B usage had been excluded. The representative in question acknowledged that he discussed these issues in this context.

With respect to the allegations that the representative was promoting empiric usage and 2mg/kg, The Liposome Company stated that it found the notion curious, that a Liposome representative would approach a consultant mircobiologist to promote empiric usage of Abelcet when it was the microbiologist's responsibility to prove the presence of a fungal infection.

The representative initially approached the complainant to discuss Abelcet in accordance with the marketing authorization. It was the company's contention that the complainant initiated specific discussions with the representative regarding issues outside the licence. The representative acknowledged that discussions extended beyond the contents of the licence, but only at the express wish of the complainant.

Abelcet was one of three lipid based formulations of amphotericin B. The indications and dosage regimens for each of the products differed. AmBisome (liposomal amphotericin B) and Amphocil (amphotericin B colloidal dispersion) were both indicated for use at lower dosages than the recommended dose of Abelcet. Additionally, none were approved for empiric usage until recently when NeXstar Pharmaceuticals Ltd gained an extension to the AmBisome licence to include empiric therapy. Medical professionals with a specific interest in fungal infections were familiar with the different lipid formulations, and were keenly aware that the dosage regimens were different. Likewise, they were also aware of the potential, at least, of using these products in an empiric environment.

The Liposome Company stated that a recent complaint was made to the Authority, Case AUTH/748/7/98, about the promotional activities of NeXstar with respect to the content of a satellite symposium. Empiric usage was openly discussed with respect to AmBisome, at a time when it was not approved by the Medicines Control Agency. The Liposome Company was extremely concerned about this and about the effect on its representatives. The complainant in this case, like many medical professionals, was well aware of these subjects and therefore questions on these subjects were often raised, as in this case. Examples of the questions asked were "Can Abelcet be used at lower dosages? Do you have any data at lower dosages? What data do you have to support empiric usage with Abelcet?".

The representative responded to the complainant's query in a fair and balanced manner. First, indicating that the recommended dosage and indications were as per the Abelcet summary of product characteristics (SPC). Then by providing an overview of the clinical development programme for Abelcet and finally, at the request of the complainant, details of treatment policies at other hospitals. At no stage did the representative promote the usage of Abelcet in these settings, nor indicate that these were company recommendations.

Following these discussions, it was verbally agreed during the meeting between the consultant microbiologist and the representative that abstracts and guidelines (including guidelines from the other hospital) would be sent to the consultant subsequent to the meeting. In order to maintain a high standard of ethical conduct the representative fulfilled the complainant's request by sending the information in a fast and efficient manner. A copy of the approved SPC was also sent. The representative did not provide written comments, advice or an opinion on the documents provided.

The Liposome Company stated that it had considered this matter bearing in mind the requirements of Clause 2, 3.2, 7.2 and 15.2 of the Code.

Clause 2: Discredit to and Reduction of Confidence in the Industry

The Liposome Company stated that the reprints that the complainant received were copies of abstracts and published papers which were all in the public domain, with the exception of the guidelines from the other hospital. The company received permission from the other hospital to provide a copy of the guidelines should a medical query of this nature be received. All the documents provided were verbally requested by the complainant. The materials provided and the role of the representative in providing these documents could not, in this context, be said to bring discredit to the industry. The representative acted in a professional manner by providing solicited information in a fast and efficient manner.

Clause 3.2: Marketing Authorization

The Liposome Company stated that the representative promoted the product in accordance with the terms of the marketing authorization by promoting Abelcet for use in intensive care and for patients with fungal infections. The Liposome Company acknowledged that discussions extended beyond the licence, but only at the specific request of the consultant microbiologist. In this context it could not be construed as promotion but as scientific service.

Clause 7.2: Information, Claims and Comparisons

The Liposome Company stated that the representative responded to specific queries that the complainant raised. Had he not provided the complainant with up-to-the-minute publications, abstracts and guidelines, as requested, he would have provided inaccurate and misleading information. Consequently, he would have breached the Code if he had not acted in the manner in which he did.

Clause 15: Representatives

The Liposome Company stated that the representative responded to specific queries that the complainant raised. Had he not provided the complainant with accurate information as requested, in the manner in which he requested it, then the representative would have been acting in an unprofessional manner. A high standard of ethical conduct would not have been maintained. The Liposome Company provided a copy of the representatives' briefing material.

PANEL RULING

The Panel noted that Clause 1.1 of the Code stated that the definition of promotion did not include replies made in response to individual enquiries from members of the

health professions so long as the response related solely to the subject matter of the enquiry, was accurate, did not mislead and was not promotional in nature. In the Panel's view, it was difficult to justify that representatives could reply to such enquiries without it being seen as promotional, given that a representative's role was primarily to promote medicines.

The Panel noted the concern expressed by The Liposome Company that it had been hindered in its investigation because the identity of the complainant had not been confirmed.

The Panel noted that the accounts differed. The complainant stated that the representative had promoted the empiric use of Abelcet and told him to ignore the data sheet and use the product at a dose of 2mg/kg/day. The representative stated that he had replied to questions asked of him by the complainant with a copy of the guidelines from the other hospital. These guidelines referred to the empiric use of Abelcet 2mg/kg/day. The licensed dose of Abelcet was 5mg/kg/day in known fungal infections.

The Panel examined the representatives' briefing material which had been provided with an accompanying explanation as to the training of representatives. For educational purposes representatives were provided with copies of abstracts and published papers on all of the modified amphotericin B products irrespective of whether the information was within the terms of the marketing authorization. Each abstract or paper was given to the representatives for information purposes only. Section 10 of the Abelcet and Fungal Infections Training Programme stated under the heading "Clinical Indications" that "Due to the ability to deliver high doses without therapy-limiting side effects, Abelcet may have a role in the earlier treatment of fungal infections and not just in patients with renal disease, eg in the empiric treatment of a suspected fungal infection, but this has not yet been established." There was no indication that this information was not to be used promotionally.

The Panel considered that it was difficult to know exactly what had transpired between the parties. The complainant had been left with the impression that the product could be used empirically at 2mg/kg/day. This would have been reinforced by the subsequent provision of the guidelines. The Panel noted that extreme dissatisfaction was necessary on the part of a complainant before he or she was moved to submit a complaint. However, given the parties' differing accounts, the Panel was not in a position to determine precisely what had been said. The Panel therefore ruled no breach of Clause 15.2 of the Code. The Panel also ruled no breach of Clauses 2, 3.2 and 7.2 of the Code.

The Panel acknowledged that the use of anti-fungal therapy was a complex area of medicine and that representatives might well be asked questions about unlicensed uses of their company's medicines. In the Panel's view it was reasonable that representatives should know about the development of the medicines they promoted. Companies should give instructions, clearly differentiating between information that could be used promotionally and information which was for the representative's personal education. The Abelcet briefing material was inadequate in this regard and in the Panel's view would be likely to lead to a breach of the Code. The Panel therefore ruled a breach of Clause 15.9 of the Code.

Complaint received **7 August 1998**

Case completed **9 October 1998**

CASE AUTH/757/8/98

CONSULTANT CHEST PHYSICIAN v GLAXO WELLCOME

"Dear Doctor" letter

A consultant chest physician complained on behalf of a general practitioner about a letter entitled 'The use of inhaled corticosteroids in childhood asthma' which had been sent to GPs in Northern Ireland. The letter had been signed by seven paediatricians in the province and had been sent on plain, unheaded, paper. The letter commented favourably about all inhaled steroids but singled out Glaxo Wellcome's product fluticasone (Flixotide) for particular praise. The complainant stated that Glaxo Wellcome had facilitated the development and distribution of the letter and this should have been made clear.

The Panel considered that the letter was a legitimate response to an article of a sensational nature in the Sunday World newspaper which might have adversely affected the continuing treatment of children on fluticasone. The Panel noted that the letter did not refer to the brand name Flixotide or mention Glaxo Wellcome.

The Panel considered that the role of Glaxo Wellcome in the development and distribution of the letter amounted to sponsorship which technically ought to have been declared on the letter. A breach of the Code was ruled.

The Panel considered that the nature of the letter and the reasons for it made it more akin to a response to an erroneous article which, if certain conditions were met, was exempt from the Code. In the particular circumstances it did not amount to promotion of fluticasone and therefore did not constitute disguised promotion nor require prescribing information. The Panel ruled no breach of the Code.

COMPLAINT

A consultant chest physician complained on behalf of a general practitioner about an unheaded letter entitled "The use of inhaled corticosteroids in childhood asthma"

which had been sent to GPs in Northern Ireland. The signatories of the letter were seven paediatricians in the province. The complainant stated that although the letter commented favourably about all inhaled steroids, fluticasone was singled out for specific praise. The complainant stated that the round table meeting at which the letter was formulated had been sponsored by Glaxo Wellcome UK Limited. The letter was mailed to GPs and this was paid for by Glaxo Wellcome. The complainant believed that this should have been made clear in the text or the letter should have been sent out on Glaxo Wellcome paper. The document purported to be independent but the test of this would be if any other company would have sponsored the same letter. The complainant thought not.

RESPONSE

Glaxo Wellcome stated that on Sunday, 5 April 1998, a very unbalanced article appeared in the Northern Ireland edition of the Sunday World, in which it was implied that Flixotide (fluticasone) might represent another thalidomide. A copy of this article was provided, together with a copy of a second article which the newspaper published later to at least partially redress the balance. Glaxo Wellcome provided a copy of a letter which it sent shortly afterwards to general practitioners, practice nurses and community pharmacists in Northern Ireland, with copies to the chief medical and pharmaceutical officers in the province, to directors of public health and pharmaceutical care at the regional health boards and the Chairman of the General Medical Services Committee.

The original article had considerable impact in some parts of Northern Ireland, with concerned parents visiting their general practitioners to have their children's treatment stopped. This led to concern among general practitioners in affected areas, not least because it represented a loss of patient confidence in the care that they were receiving - the association between Flixotide and both thalidomide and BSE caused predictably emotive reactions.

In conversation with the company's respiratory therapy leader in Northern Ireland, a consultant paediatrician expressed concern that this might lead to patients stopping their treatment abruptly, with possible serious consequences. Other paediatricians in the province shared his concern and in order to help to allay the fears of parents agreed to write a letter to general practitioners in Northern Ireland.

Glaxo Wellcome stated that its respiratory therapy leader and its local hospitals representative arranged a room at an hotel and the consultant paediatrician and another consultant met there and wrote the letter, which met with their colleagues' approval. As was evident from reading the letter, it referred to the recent newspaper article and the comparisons it made between fluticasone and thalidomide. Indeed, the authors were at pains to point out to the respiratory therapy leader that this letter was independent and represented their beliefs and not those of any company. Hence their efforts to make the letter absolutely balanced - the authors owed no allegiance to any companies. There was a very short paragraph regarding the paediatricians' own experience of using fluticasone in childhood asthma. However, most of the letter was devoted to a balanced discourse on the use of inhaled corticosteroids in childhood asthma, with reference to both the British Guidelines on Asthma Management and the recent bulletin from the CSM/MCA, "Current Problems in Pharmacovigilance: Focus on Corticosteroids". Glaxo Wellcome submitted that there were very helpful references to reducing the dose to the lowest effective dose, monitoring the height of children using any inhaled corticosteroid and the potential for all inhaled corticosteroids to have systemic side effects, especially when used at high doses over a prolonged period.

Glaxo Wellcome's role consisted of facilitating the writing of the letter by arranging a meeting room and covering the postage costs for the letter (through a local mailing company), which was mailed on or about 6/7 July.

The letter itself was prepared by the secretary of one of the authors and was circulated by hand to the other paediatricians by Glaxo Wellcome's respiratory therapy leader and local hospitals representative before being despatched. It was typed on plain, unheaded paper as the signatories considered that this was most appropriate given that they were themselves from a number of different hospitals.

Although the company paid for the postage, it had no editorial control over the contents of the letter, and on reading the letter it appeared to be balanced and impartial. Any references to fluticasone were clearly to help general practitioners and practice nurses to allay the fears of the parents of the asthmatic children in their care, with respect to the issues raised by the newspaper article.

The material itself was not sponsored in any way by Glaxo Wellcome and it believed that there had not been a breach of Clause 9.9 of the Code. Glaxo Wellcome did not believe that this independently written letter could be considered to be promotional and believed, therefore, that no breach of Clause 10.1 had occurred.

PANEL RULING

The Panel considered that the sensational nature of the article in the Sunday World and the possible effect of it on the continuing treatment of children on fluticasone (Flixotide) justified the circulation of a response. It was understandable that particular reference should have been made in the letter to fluticasone because Flixotide had been the subject of the article in question. The Panel noted that the letter referred only to fluticasone, no mention being made of the brand name Flixotide or of Glaxo Wellcome.

The Panel considered that the role of Glaxo Wellcome in facilitating the development and distribution of the letter amounted to sponsorship. Clause 9.9 of the Code required that all material relating to medicines and their uses which was sponsored by a pharmaceutical company must clearly indicate that it had been sponsored by that company. That had not been done and technically the company was in breach of Clause 9.9 of the Code. The Panel ruled accordingly.

Where such a letter referred in positive terms to the sponsor's product, it would normally be regarded as promotional material and required to bear prescribing information for the product. The question of whether it amounted to disguised promotion would also be an issue.

The Panel considered, however, that the nature of the letter and the reasons for it made it more akin to a response to an erroneous article in a professional journal which was exempt from the Code if certain conditions were met. In the particular circumstances, the Panel did not consider that the letter amounted to the promotion of fluticasone and ruled no breach of either Clause 4.1 or Clause 10.1.

Complaint received	**13 August 1998**
Case completed	**16 October 1998**

CASE AUTH/759/8/98

GLAXO WELLCOME v MERCK SHARP & DOHME

Maxalt mailing

Glaxo Wellcome complained about a mailing for Maxalt (rizatriptan) issued by Merck Sharp & Dohme which compared Maxalt with 100mg sumatriptan, Glaxo Wellcome's product Imigran.

Glaxo Wellcome alleged that the claim "... Maxalt 10mg tablets provided faster headache relief within two hours than sumatriptan 100mg" was misleading as it implied that rizatriptan was faster than Imigran 100mg at each individual time point from 30 minutes through to 120 minutes. This was not however the case. A study had shown no significant difference at 30, 60 and 90 minutes. Other studies also showed no significant differences. The Panel considered that overall there was data to show a trend in favour of rizatriptan 10mg compared with sumatriptan 100mg. One study had recorded a statistically significant advantage for rizatriptan at 1 hour. The Panel considered, however, that given the data the claim was misleading and a breach of the Code was ruled.

In relation to the claim "More patients became pain free compared to sumatriptan 100mg", Glaxo Wellcome said that although it was true for the study to which it was referenced it did not reflect all of the available data. A study comparing rizatriptan with Imigran 50mg found no significant benefit for rizatriptan at 90 and 120 minutes. As this study compared against the lower strength of Imigran one would expect rizatriptan to show an improved benefit rather than less. The Panel noted that the claim was referenced to a study involving 1099 patients. Glaxo Wellcome accepted that the claim was true for that study. Subsequent text in the mailing qualified the claim. The Panel considered that the claim was not unacceptable and no breach of the Code was ruled.

Glaxo Wellcome alleged that the claim "Within two hours, 90% of attacks were relieved in a typical patient with Maxalt 10mg tablets", gave a misleading impression that rizatriptan had a 90% efficacy rate which was not so. The data came from an extension study and hence exaggerated the true efficacy rate because it enrolled patients who had had success with the medicine in the controlled part of the trial rather than a heterogeneous population. The Panel considered that the claim did not made it sufficiently clear what was meant by the phrase "a typical patient". In the Panel's view some readers would gain the impression that the response rate was 90% for all patients. This was not so. As the Panel understood it, patients who elected to continue in a long-term study and were randomly allocated to receive Maxalt 10mg had 90% of their attacks relieved in 2 hours. The Panel considered that on balance the claim was misleading and ruled a breach of the Code. Upon appeal by Merck Sharp & Dohme, the Appeal Board noted that 84% of patients in the acute studies continued with the long-term extension study. The Appeal Board expressed the opinion that patients were more likely to continue to the extension study if they had benefited from the treatment received in the acute studies. In the Appeal Board's view, some readers would gain the impression from the claim in question that the response rate for Maxalt 10mg was 90% for all patients. This was not so. This figure only referred to those patients who had elected to continue long-term treatment. Acute studies showed that 67-77% of patients responded to therapy. The Appeal Board considered that the claim was misleading and upheld the Panel's ruling of a breach of the Code.

Glaxo Wellcome noted that the claim "With significantly fewer drug-related adverse events for patients on Maxalt 10mg tablets than for patients on sumatriptan 100mg..." was referenced to data on file. An abstract from what was believed to be the same study noted that rizatriptan had a "comparable incidence of central side effects (dizziness, somnolence) relative to sumatriptan 100mg and numerically fewer patients with chest pain". Another comparative study noted that the incidence of adverse effects on rizatriptan was 48% compared with 46% on Imigran. Glaxo Wellcome alleged that the claim did not reflect the published data. The Panel noted that the claim was specific in that it referred to drug related adverse events and clearly compared the 10mg Maxalt dose with the 100mg sumatriptan dose. The Panel considered that the claim was not misleading. It was an accurate reflection of the data. No breach of the Code was ruled.

Glaxo Wellcome alleged that the claim "Maxalt Melt 10mg – a new alternative to oral tablets" misled the reader into assuming that the claims for efficacy and speed of onset were the same for the Melt as for the tablet formulation. There was no mention that the onset of action of Maxalt Melt was slower than that of the ordinary tablet. The Panel considered that readers would assume that the onset of effect of Maxalt Melt was similar to Maxalt but according to the summary of product characteristics (SPC) this was not so. The SPC stated that the headache relief with Maxalt occurred as

early as 30 minutes and that the onset of the effect occurred as early as 60 minutes following dosing with Maxalt Melt. The Panel noted that the relief rates in patients treated with Maxalt Melt were approximately 66%. The Panel considered that the letter was misleading as it implied that the features of Maxalt Melt were similar to Maxalt and according to the SPC this was not so. A breach of the Code was ruled.

Glaxo Wellcome UK Limited complained about a Maxalt (rizatriptan) mailing (ref 07-99 MXT.98.GB.45128.L.16M. HO.798) sent to hospital and retail pharmacists by Merck Sharp & Dohme Limited. The material compared Maxalt with 100mg sumatriptan, Glaxo Wellcome's product Imigran.

1 Claim "...Maxalt 10mg tablets provided faster headache relief within two hours than sumatriptan 100mg"

The claim was referenced to data on file.

COMPLAINT

Glaxo Wellcome alleged that the claim was misleading in breach of Clause 7.2 of the Code as it implied that rizatriptan was faster than Imigran 100mg at each individual time point from 30 minutes through to 120 minutes. This however was not the case. There was no significant difference between rizatriptan and Imigran at 30 minutes, 90 minutes and 120 minutes in a study by Visser *et al* 1997.

In addition, without providing the median time to relief for the two agents, it was impossible for the reader to evaluate how much faster rizatriptan was than Imigran according to this analysis, and therefore whether the claim had any meaningful clinical relevance.

Furthermore, the claim referred to a time-to-first-relief analysis, (a cumulative percentage of patients first reporting relief within 2 hours), but it was not made clear on the mailing that this was a different method of analysis than that used traditionally.

Finally, the claim did not reflect all of the available data. There were two other comparative trials of rizatriptan and Imigran. One of these studies, (Visser *et al* 1996), although smaller, showed no difference between rizatriptan 10mg and Imigran 100mg at any of the time points measured. In fact the authors concluded that the treatments were "equiefficacious".

The other study (Norman 1998) compared rizatriptan 10mg with the lower strength of Imigran (50mg) and again found no significant difference between the two treatments at 30, 60, 90 or 120 minutes.

It was therefore surprising that Merck Sharp & Dohme could claim faster relief of pain than Imigran 100mg when it had not been able to show a significant difference against Imigran 50mg (ie half the strength).

RESPONSE

Merck Sharp & Dohme submitted that the claim was based on the primary end-point of the Maxalt vs sumatriptan comparison study (ref no. 030), which showed a statistically significant difference ($p<0.05$) in terms of the age adjusted time to headache relief analysis. This type of analysis was commonly used in the analysis of clinical trials, and was also known as survival analysis or life table analysis. The concept and methods of such analyses were discussed in medical statistical textbooks (eg DG Altman, Practical Statistics for Medical Research) and were currently the subject of an ongoing series in the BMJ, Statistics Notes (first in series published 15 August 98). The concept (although different methods) had been utilised by Glaxo Wellcome in some migraine studies with sumatriptan.

In the 030 study the analysis compared the time that patients first reported headache relief at time points up to 2 hours for Maxalt vs sumatriptan 100mg. The analysis was considered more appropriate than a number of comparisons at different time points for a number of reasons.

a It used all the available data up to 2 hours.

b It avoided the statistical problem of making a number of comparisons within the same study at the different time points ("multiplicity"). Such multiple comparisons increased the chance of finding $p<0.05$ merely by chance. A number of statistical methods existed to allow for multiplicity when making such multiple comparisons. However, survival analysis (ie time to headache relief analysis) was a perfectly valid alternative.

c It accommodated "censoring". The analysis included all the data available. Data from early time points were included even when those from later time points were not available.

d It increased the statistical power.

The method used for the analysis, a variation of Cox regression, produced a summary statistic, the "hazard ratio", which quantified the treatment comparison. The hazard ratio for Maxalt vs sumatriptan 100mg was 1.21 ($p=0.032$). This meant that for any patient with a headache at a particular time point they were approximately 20% more likely to get relief of their headache within the next unit of time (second, minute) with Maxalt than with sumatriptan 100mg.

Merck Sharp & Dohme then dealt with each of Glaxo Wellcome's comments in turn. The claim was substantiated by the time to relief analysis, and, quite deliberately, no claim was made within this statement with regard to specific individual time points. In fact, the difference in rates of headache relief at 1 hour was statistically significant ($p=0.01$) and whilst differences between Maxalt and sumatriptan 100mg in study 030 were not statistically significant at all the individual time points, Maxalt provided numerically superior pain relief at all time points up to and including 2 hours.

The letter was intended as a summary of the potential attributes of Maxalt. The claim could be substantiated, but the letter was intended to be a brief summary of the information available. The hazard ratio conveyed clinical meaning to the analysis that could be discussed with healthcare professionals and individual patients alike. Merck Sharp & Dohme argued that it was not usual practice to detail the statistical analysis underlying promotional claims in a letter of this nature. Merck Sharp & Dohme did not consider that it was necessary, or

indeed desirable, to do so. As always, the information to substantiate the claim was available on request.

Merck Sharp & Dohme was astonished that Glaxo Wellcome criticised the phase III data by quoting a small dose ranging phase II study. On this basis one could criticise most claims based on phase III data for any licensed product. The study comparing Maxalt and sumatriptan 100mg to which Glaxo Wellcome referred (Visser *et al* 1996) was a dose ranging study with 449 patients, and used encapsulated rizatriptan and sumatriptan to maintain the blind. Since these were not the marketed formulations of the medicine this study had not been used in promotion. The treatment groups were also much smaller than the 030 study of 1099 patients used to substantiate the claim With the smaller Visser study there was much less statistical power to detect a difference between the Maxalt 10mg and sumatriptan 100mg groups, than in the larger 030 study. However, as could be clearly seen from the graph in figure 1 of Visser *et al's* paper, Maxalt was numerically superior to sumatriptan 100mg throughout the 2 hour period.

The comparison made in the claim was clearly with sumatriptan 100mg. However, Glaxo Wellcome again tried to disparage the claim by referring to specific time points, but this time with reference to the 046 study comparing Maxalt with sumatriptan 50mg. In this study, Maxalt was statistically significantly superior to sumatriptan 50mg in a time to relief analysis (p=0.046, hazard ratio 1.14). Again, at all time points within 2 hours Maxalt was numerically superior to sumatriptan 50mg, It was unfortunate that Glaxo Wellcome did not seem to have provided all the slides from the presentation, which would have made this point clear.

In summary the claim that "Maxalt tablets provided faster headache relief within 2 hours than sumatriptan 100mg" was supported by the time to headache relief analysis. It provided a valid summary of the outcome of the analysis. In any event, and notwithstanding that it was not the comparison made in the letter, the statement would apply equally well to sumatriptan 50mg.

PANEL RULING

The Panel noted that in study 030, to which the claim was referenced, significantly more patients reported pain relief at one hour in the rizatriptan 10mg group than in the sumatriptan 100mg group (36.6% v 27.9% respectively; p=0.01). At the other time points, 0.5, 1.5 and 2 hours, there was a numerical difference in favour of rizatriptan but this did not reach statistical significance.

Viser *et al* (1996) was a dose ranging study using encapsulated products in 449 patients. The proportion of patients whose condition improved showed no statistically significant differences between rizatriptan 10mg and sumatriptan 100mg at 0.5, 1, 1.5 or 2 hours although numerical differences in favour of rizatriptan were recorded at all time points.

In study 046 the comparisons made were between rizatriptan 10mg and sumatriptan 50mg. At 0.5, 1, 1.5 and 2 hours the percentage of patients reporting pain relief showed numerical differences in favour of rizatriptan but none of these reached statistical significance.

The Panel considered that overall there was data to show a trend in favour of rizatriptan 10mg compared with sumatriptan 100mg. One study (030) had recorded a statistically significant advantage for rizatriptan 10mg at 1 hour. The Panel considered, however, that given the data the claim "Maxalt 10mg tablets provide faster headache relief within 2 hours than sumatriptan 100mg" was misleading. A breach of Clause 7.2 was ruled.

2 Claim "More patients became pain free compared to sumatriptan 100mg".

COMPLAINT

Glaxo Wellcome alleged that although the claim was true for the study to which it was referenced (at 90 minutes), it again did not reflect all of the available data. The Norman 1998 study comparing rizatriptan with Imigran 50mg found no significant benefit for rizatriptan at 90 and 120 minutes in this measure. As this study compared against the lower strength of Imigran, one would expect rizatriptan to show an improved benefit rather than less benefit. A breach of Clause 7.2 was alleged.

RESPONSE

Merck Sharp & Dohme submitted that the time point for the claim was qualified by the text which followed it. This was "Compared to sumatriptan 100mg, Maxalt 10mg allowed 33% more patients to become completely pain free at 90 minutes (p=0.038)". At the other time points assessed up to 2 hours Maxalt was numerically superior (p>0.05) vs sumatriptan 100mg.

Once again, Glaxo Wellcome made reference to the comparison with sumatriptan 50mg in the 046 study, which was totally irrelevant as it was not the comparison made in the letter. In this study Maxalt was numerically superior to sumatriptan 50mg at all time points up to 2 hours and this was statistically significant at 1 hour. The time to pain free analysis in this study was borderline in terms of significance (p=0.051).

In summary the claim was true and valid. It was in no way misleading as all studies showed Maxalt to be numerically superior in terms of the pain free endpoint to sumatriptan at the 50 or 100mg dose.

PANEL RULING

The Panel noted that this claim was referenced to the 030 study which had involved 1099 migraine sufferers. Glaxo Wellcome accepted that the claim was true for the study to which it was referenced. Subsequent text in the letter had qualified the claim.

The Panel considered that the claim was not unacceptable and no breach of Clause 7.2 of the Code was ruled.

3 Claim "Within two hours, 90% of attacks were relieved in a typical patient with Maxalt 10mg tablets"

COMPLAINT

Glaxo Wellcome alleged that the claim gave a misleading

impression that rizatriptan had a 90% efficacy rate which was not so.

The data came from an open, long-term extension study and hence exaggerated the true efficacy rate of the medicine because it typically enrolled patients who had had success with the medicine in the controlled part of the trial rather than a heterogeneous population. If a "typical" patient it was a typical responder at best. It also did not reflect the published data seen in other placebo controlled studies of rizatriptan, nor indeed the data given on the summary of product characteristics (SPC) for rizatriptan where response rates of 67-77% were given at 2 hours. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Merck Sharp & Dohme stated that studies of the acute treatment of migraine were usually based on each patient treating a single attack. Treatment of such single attacks (as in its own acute studies), although useful in its own right, did not give an indication of what the true clinical experience might be. Patients did not in real life treat one migraine attack with one treatment and then move on to a different treatment. The SPC stated a 2 hour headache relief rate for patients taking rizatriptan 10mg of 67-77% in acute studies. The figure of 90% referred to the median number of attacks relieved within 2 hours in the long-term extension study. Therefore, in the acute studies 7 out of 10 patients achieved headache relief at 2 hours in the single attacks treated. However, in long-term use, treating many attacks, patients could expect 9 out of 10 migraine attacks to be relieved by Maxalt by 2 hours. Glaxo Wellcome referred to such long-term extensions as "a clinical situation closely resembling clinical use" in their publication regarding Tolerability And Efficacy Of Naratriptan Tablets With Long-Term Treatment (6 months).

The long-term extension study referred to did not specifically follow up already proven responders. At completion of the double-blind phase of each of three studies, subjects were randomly allocated to receive rizatriptan 5mg, rizatriptan 10mg or usual care. As the patients and investigators remained blinded to the original treatment allocation in the acute phase of the study, there was no opportunity for bias.

Merck Sharp & Dohme believed that the claim accurately reflected the efficacy of rizatriptan that could be expected in long-term use, in a situation that both Merck Sharp & Dohme and Glaxo Wellcome believed, in many ways, more closely reflected clinical practice than the acute studies.

PANEL RULING

The Panel noted that the SPC referred to response rates two hours after treatment as being 67-77% with the 10mg tablet, 60-63% with the 5mg tablet and 23-40% with placebo.

The panel noted that the claim in question referred to attacks in a typical patient. The Panel considered that the claim did not make it sufficiently clear what was meant by the phrase "a typical patient". Merck Sharp & Dohme submitted that the phrase referred to patients who had completed the double blind phase of studies and had elected to continue in a study extension. In the Panel's view some readers would gain the impression that the response rate was 90% for all patients. This was not so. As the Panel understood it, patients who elected to continue in a long-term study and randomly allocated to receive Maxalt 10mg had 90% of their attacks relieved in 2 hours. The Panel considered that on balance the claim was misleading and ruled a breach of Clause 7.2 of the Code.

APPEAL BY MERCK SHARP & DOHME

Merck Sharp & Dohme believed that the use of data from long-term extension studies provided valuable and relevant information for both pharmacists and doctors. This form of data more accurately reflected the true clinical picture and had been used in this therapeutic area by Glaxo Wellcome to present data for both naratriptan and sumatriptan.

For the purposes of both the acute and the long-term studies, a typical (migraine) patient was described as a patient who experienced more than one migraine attack per month but not more than eight attacks per month. This was taken in the context of a patient who had been diagnosed with migraine (as defined by the International Headache Society criteria) for a minimum of six months. These were the entry criteria for both the acute and long-term studies. All patients from the acute studies were offered the option to continue into the long-term study irrespective of their treatment in the acute study. Patients entering the long-term study were randomised to one of three treatment groups in the order that they completed the acute study to avoid bias. Therefore the company submitted that the patients entering the long-term study were still representative of typical migraine patients.

The study results showed that 84% of patients from the acute studies continued into the long-term study. Six of the 31 sites involved in the acute studies elected not to take part in the long-term study and this was a major contributing factor to the 16% of patients not continuing into the long-term extension. Therefore the dropout in terms of patients not continuing into the long-term study was predominantly influenced by logistical reasons ie study sites electing not to participate in the long-term study, rather than response or lack of response to treatment.

Merck Sharp & Dohme therefore believed that the claim accurately reflected the efficacy of rizatriptan in long-term use and more closely resembled clinical practice. Patients who entered the acute studies were typical migraine patients. Patients who entered the long-term study were not selected on the basis of either the treatment they received or their response to treatment in the acute study and therefore the typical nature of the patient was preserved. It was therefore clear that the claim was a fair and true reflection of the available clinical data.

APPEAL BOARD RULING

The Appeal Board noted the submission that 84% of patients in the acute studies continued into the long-term extension study. The company submitted that the patients entering the long-term study knew that they

would all receive active treatment, and that they were representative of those in the acute phase. The Appeal Board noted that no detailed data had been supplied to support the company's submission regarding the comparability of the two populations.

The Appeal Board expressed the view that patients were more likely to continue to the long-term extension study if they had benefited from the treatment received in the acute studies.

The Appeal Board noted that the Maxalt SPC referred to response rates two hours after the acute treatment of migraine as being 67-77% with the 10mg tablet, 60-63% with the 5mg tablet and 23-40% with placebo. The percentages thus referred to the number of patients who when treated for one migraine attack, experienced pain relief.

The claim in question "Within two hours, 90% of attacks are relieved in a typical patient with Maxalt 10mg tablets" referred to long-term data and the number of attacks that would be relieved in any one patient over time with Maxalt 10mg.

In the Appeal Board's view some readers would gain the impression from the claim in question that the response rate for Maxalt 10mg was 90% for all patients. This was not so. This figure only referred to those patients who had elected to continue long-term treatment. Acute studies showed that 67-77% of patients responded to therapy. The Appeal Board considered that the claim was misleading and upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal was unsuccessful.

4 Claim "With significantly fewer drug-related adverse events for patients on Maxalt 10mg tablets than for patients on sumatriptan 100mg..."

COMPLAINT

Glaxo Wellcome noted that this claim was referenced to data on file. However, an abstract from what was believed to be the same study (Visser *et al* 1997), presented at the International Headache Congress (IHC) in 1997, noted that rizatriptan had a "comparable incidence of central side effects (dizziness, somnolence) relative to sumatriptan 100mg and numerically fewer patients with chest pain".

In addition, a further published comparative study (Visser *et al* 1996) noted that the overall incidence of adverse events on rizatriptan 10mg was 48% compared with 46% on Imigran 100mg. Finally, there was no mention of the fact that rizatriptan 10mg was associated with a similar incidence of adverse events as Imigran 50mg (Norman 1998).

Glaxo Wellcome alleged that the claim did not reflect the published data in breach of Clause 7.2 of the Code.

RESPONSE

Merck Sharp & Dohme submitted that the claim was in relation to total drug related adverse events. No claim had been made with regard to individual central side effects or other specific body system adverse effects. Although the incidence of central side effects was indeed comparable, the incidence of many other adverse experiences eg nausea was less, making the difference in the totals statistically significant in favour of Maxalt.

As discussed above, the Visser 1996 study was small in comparison to study 030 and used encapsulated drug rather than the marketed formulation. The interpretation of the adverse event data was also complicated by the fact that patients could also take a further different dose if they had not responded by 2 hours. Consequently, 48 patients took rizatriptan 10mg only and 33 patients sumatriptan 100mg only. Because of the small number of patients, no formal statistical analysis of the adverse event data was performed for this study. In the complaint, Glaxo Wellcome referred to the total (both drug-related and non-drug-related) adverse events, rather than the drug-related adverse events referred to in the claim. Since study 030 was so much larger and used marketed formulation, it provided a much better indication of the adverse event profile than the Visser study.

The comparison here was clearly in relation to the 100mg dose of sumatriptan, and Glaxo Wellcome's comment regarding the tolerability of the 50mg dose was not relevant.

PANEL RULING

The Panel noted the comments made by Merck Sharp & Dohme about the Visser 1996 study which referred to adverse events whether considered related or unrelated to the test medication. Escape medications were allowed at 2 hours.

The Panel noted that the claim was specific in that it referred to drug related adverse events and clearly compared the 10mg Maxalt dose with the 100mg sumatriptan dose. The Panel considered that the claim was not misleading. It was an accurate reflection of the data in study 030. No breach of Clause 7.2 was ruled.

5 Claim "Maxalt Melt 10mg - a new alternative to oral tablets"

COMPLAINT

Glaxo Wellcome alleged that the mention of Maxalt Melt within the letter misled the reader into assuming that the claims for efficacy and speed of onset were the same for the Melt as for the tablet formulation. There was no mention within the letter that the onset of action of the Maxalt Melt was slower than that of the ordinary tablet, hence misleading the reader into believing the Maxalt Melt also had an onset from 30 minutes. As stated in the SPC the Maxalt Melt had an onset from 60 minutes. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Merck Sharp & Dohme stated that the claim highlighted an alternative new method of taking oral tablets without the need for water. No claim or implication was made for the speed of onset of action for the melt formulation. To quote the SPC more fully "... the efficacy of the oral

lyophilisate formulation was comparable to that observed in similarly designed trials of Maxalt tablets. Onset of effect was as early as 60 minutes following dosing. By two hours post dosing, relief rates in patients treated with Maxalt Melt oral lyophilisates were 66%..." A larger study presented at the Migraine Trust meeting on 2 September 1998 had now demonstrated the onset of action as early as 30 minutes with the wafer formulation, ie response rates for Maxalt Melt in terms of both headache relief and pain free were significantly superior to placebo at the half hour time point (a summary of the study was provided).

PANEL RULING

The Panel considered that readers of the letter would assume that the onset of effect of Maxalt Melt was similar to Maxalt but according to the SPC this was not so. The SPC stated that headache relief with Maxalt occurred as early as 30 minutes - as mentioned in the letter in question. The SPC stated that the onset of the effect occurred as early as 60 minutes following dosing with Maxalt Melt. The Panel noted that the relief rates in patients treated with Maxalt Melt were approximately 66%.

The Panel considered that the letter was misleading as it implied that the features of Maxalt Melt were similar to Maxalt and according to the SPC this was not so. A breach of Clause 7.2 of the Code was ruled.

Complaint received 19 August 1998

Case completed 15 January 1999

CASE AUTH/762/9/98

SHIRE v ZENECA PHARMA

Zoladex journal advertisement

Shire complained about a journal advertisement for Zoladex (goserelin) issued by Zeneca Pharma which compared the efficacy and tolerability of Zoladex via a subcutaneous depot injection with intranasal buserelin in assisted conception, detailing some results from a clinical study. Shire marketed an intranasal buserelin, Suprecur Nasal Spray. The advertisement stated that "Significantly less tiredness, headache and abdominal pain were reported in the first 2 to 3 weeks of treatment when compared to intranasal buserelin" and implied that the difference in side effects and the convenient administration of goserelin as a depot injection reduced the stress for patients.

Shire said that the study referred to used a buserelin dosage regimen of 200 micrograms six times a day whereas the UK licensed dose was 150 micrograms four times a day. With the higher dose one would realistically expect a higher incidence of side effects. Shire alleged a breach because claims for Zoladex efficacy versus buserelin must reflect the dosage stated in the Suprecor Nasal Spray data sheet.

The Panel noted that the study stated that for the successful outcome of IVF treatment it was important to minimize the stress and inconvenience related to the treatment as much as possible and that many patients found the administration of the intranasal buserelin spray several times a day to be inconvenient and concluded that the difference in side effects observed between the two patient groups was due to the different mode of administration. The Panel noted that the advertisement stated that Zoladex was as effective as daily injections or intranasal buserelin in terms of pituitary down regulation, oocyte recovery and pregnancy rate per embryo transfer. The Panel considered that it was misleading to claim equivalent efficacy when the dose of intranasal buserelin was the maximum total daily dose at an unlicensed dosage regimen, ie in six divided doses and not four as stated on the data sheet. The Panel ruled a breach of the Code. Upon appeal by Zeneca, the Appeal Board noted that in assisted conception Zoladex or buserelin were administered in order to achieve pituitary down-regulation. The Suprecur (buserelin) data sheet stated that to achieve pituitary down-regulation a total daily dose of 600 micrograms should be given although some patients might require a total daily dose of 1200 micrograms. The Appeal Board noted that although the study had used a buserelin dose of 1200 micrograms in all women, this would minimize the risk of treatment failure in the small proportion of women who would not respond to 600 micrograms daily. Zoladex had thus been compared with the maximum licensed dose of buserelin. The study showed that the products were equally effective in suppressing pituitary gonadotrophin secretion. The Appeal Board considered, therefore, that it was not misleading to claim that Zoladex was as effective as buserelin and no breach of the Code was ruled. The appeal on this point was therefore successful.

Shire stated that the claims for a significantly better side effect profile for goserelin versus buserelin in the study were based on a questionnaire with a subjective estimation scale of the quality of a limited number of different complaints completed by patients post therapy. Shire alleged that this was not a validated methodology to compare therapy to evaluate side effect profiles. Shire alleged that the advertisement was inaccurate and misleading as to any possible differences between goserelin and buserelin. The Panel considered that an assessment of side effects by the

patient was necessarily subjective but this did not in itself negate the value of the data. The Panel noted that the claim in the advertisement relating to the comparative incidence of side effects was that with Zoladex "Significantly less tiredness, headache and abdominal pain were reported in the first 2 to 3 weeks of treatment when compared to intranasal buserelin". In the discussion section of the study the authors reported that the increased incidence of these side-effects might have been due to the fact that many patients found the administration of intranasal spray several times a day inconvenient. The Panel noted that the total daily dose of buserelin had been given in six divided doses and not in four divided doses as recommended in the UK data sheet. The Panel considered that with regard to the licensed dosage frequency of intranasal buserelin the comparative claim relating to side-effects was misleading and unfair. A breach of the Code was ruled. Upon appeal by Zeneca the Appeal Board noted from its previous ruling that all women had been treated with the maximum licensed dose of buserelin (1200 micrograms daily) in order to minimize the risk of treatment failures. Most women would have needed only half this dose of buserelin to achieve pituitary down-regulation and had thus received too much buserelin for the required clinical outcome. Zeneca had not produced any information to show that buserelin dosed at 200 micrograms six times daily did not produce any more side effects than buserelin dosed at 150 micrograms four times daily, the dose which would have worked in most women. The Appeal Board considered that given the high dose and frequency of buserelin, the comparative claim regarding side-effects was misleading and the Panel's ruling of a breach of the Code was upheld. The appeal on this point therefore failed.

Shire Pharmaceuticals Ltd complained about a journal advertisement (ref 98/9211(E)) for Zoladex (goserelin) issued by Zeneca Pharma. The advertisement compared the efficacy and tolerability of Zoladex with intranasal buserelin in assisted conception detailing some results from a Finnish clinical study by Tapanainen *et al* (1993). Shire marketed an intranasal buserelin, Suprecur Nasal Spray.

The advertisement stated that "Significantly less tiredness, headache and abdominal pain were reported in the first 2 to 3 weeks of treatment when compared to intranasal buserelin." The advertisement implied that the difference in side effects and the convenient administration of goserelin as a depot injection reduced the stress for patients.

Shire alleged that the advertisement was in breach of Clauses 3.2, 7.2 and 8.1 of the Code.

1 Study used unlicensed dose of buserelin

COMPLAINT

Shire stated that the buserelin regimen cited in the paper by Tapanainen *et al* was not a licensed UK dosage regimen. The Tapanainen study referred to a buserelin dosage regimen of 200 micrograms given six times a day whereas the UK licensed dosage was 150 micrograms given four times a day. Shire stated that with the higher dose given in the study, one would realistically expect a higher incidence of side effects at the maximum dose used. The administration of the product six times a day was also inconsistent with the approved regimen of four times a day. Claims for Zoladex efficacy versus buserelin must reflect the dosage stated in the Suprecur Nasal Spray data sheet.

RESPONSE

Zeneca stated that it understood that the recommended dosage regimen in Finland for buserelin nasal spray for pituitary down-regulation in patients undergoing *in vitro* fertilisation (IVF) was 1200 micrograms daily, given in 8 puffs. Tapanainen *et al* used 1200 micrograms daily given in six divided doses. Shire, in its UK data sheet, recommended 600-1200 micrograms daily given in four divided doses (not 600 micrograms daily as suggested in its complaint). In addition, Shire in its correspondence with Zeneca had stated "UK Assisted Conception Units use a range of regimens with Suprecur nasal spray..." Zeneca stated that different centres and different countries used differing regimens for buserelin nasal spray in their protocols. The fundamental point was that Tapanainen *et al* used 1200 micrograms daily which was within the UK licensed dosage of 600-1200 micrograms daily. Zeneca, therefore, considered that it was acceptable to use the results of this study in the UK especially when one considered that, as Shire had stated, units in the UK used a range of regimens.

PANEL RULING

The Panel noted that different centres and different countries used differing regimens for buserelin nasal spray in their protocols. The Panel considered that in the UK the UK data sheet or summary of product characteristics took precedence and represented the agreed details about a product. Information from individual centres or other countries might however be of interest.

The Panel noted from the Suprecur data sheet that in pituitary desensitisation prior to ovulation induction the total daily dose of intranasal buserelin was 600 micrograms given in four divided doses spread over the waking hours. Dosage should be continued until down-regulation was achieved, ie serum oestradiol was < 50ng/l and serum progesterone was <1 microgram/l. In some patients dosages of up to 4x300 micrograms might be required to achieve these levels. The Panel noted that the higher dose gave a total daily dose of 1200 micrograms.

The paper by Tapanainen *et al* compared the efficacy of subcutaneous Zoladex and intranasal buserelin for pituitary down-regulation in patients undergoing IVF. All patients in the buserelin group received 200 micrograms six times a day. The total daily dose was thus the maximum recommended for those patients who had not achieved down-regulation on the lower total daily dose of 600 micrograms. The effects of the lower dose were not studied.

The Panel noted that the frequency of dosing of the

intranasal buserelin, as used by Tapanainen *et al*, was six times daily and not four times daily as recommended in the UK data sheet. The introduction to the Tapanainen paper included the statement that for the successful outcome of IVF treatment it was important to minimize the stress and inconvenience related to the treatment as much as possible. The Tapanainen paper stated that many patients found the administration of intranasal buserelin spray several times a day to be inconvenient and concluded that the difference in side effects observed between the two patient groups was due to the different mode of administration.

The Panel noted that the advertisement stated that Zoladex was as effective as daily injections or intranasal buserelin in terms of pituitary down regulation, oocyte recovery and pregnancy rate per embryo transfer. The Panel considered that it was misleading to claim equivalent efficacy when the dose of intranasal buserelin was the maximum daily dose at an unlicensed dosage regimen, ie six times daily. In this regard the Panel noted the statement in the paper regarding stress and inconvenience of treatment. The Panel ruled a breach of Clause 7.2 of the Code.

The Panel did not consider that the claims disparaged Suprecur Nasal Spray and no breach of Clause 8.1 was ruled.

The Panel noted that Clause 3.2 of the Code stated that "The promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics or data sheet". The advertisement did not refer to the dosage regimen for intranasal buserelin. The advertisement in question promoted Zoladex not intranasal buserelin. The Panel ruled that there was no breach of Clause 3.2 of the Code with regard to the dosage frequency of buserelin.

APPEAL BY ZENECA PHARMA

Zeneca noted that Clause 7.2 did not state that it was, by definition, misleading to make a comparison which was based on a dosage regimen which was not exactly the same as in the data sheet; nor should such a comparison be ruled misleading in all circumstances.

Zeneca contended that, in the particular circumstances of this case, in order to ensure a comparison between Zoladex with buserelin was balanced, fair and objective and therefore not misleading, it was important to compare "like with like". This was what the advertisement did on the basis of an independently conducted study of Zoladex and buserelin (Tapanainen *et al*). This study was the only available comparative study of the two agents and provided valuable information which Zeneca should be free to communicate to health professionals. On close examination of the scientific data it was clear that Zoladex was at least effective as buserelin used in the manner outlined in the data sheet. Buserelin was used in a variety of dosage regimens in the UK and around the world, one of which was used in the Tapanainen study.

With regard to the total daily dose, Zeneca stated that in this therapeutic area in order to compare "like with like" the two regimens must both fully down regulate oestradiol. Zoladex, as a depot injection, was given at just one dosage level which fully achieved this. Buserelin was given at more than one dosage level. Given at the lower total daily dose of 600 microgram it did not fully down regulate oestradiol in all patients. This was clear from the product data sheet which stated that 1200 micrograms would be needed in some patients.

Zeneca did not understand how claiming equivalence with a competitor used at its maximally effective dose could be considered to be misleading on the grounds that the product data sheet allowed it to be used at a lower, possibly less effective dose.

With regard to dosage frequency, Zeneca stated that whether the buserelin daily dose was given in four or six divided doses was irrelevant to a comparison of efficacy with Zoladex depot. Both these dosage frequencies would have similar effects on oestradiol levels and in all likelihood this would have been a factor in the approval in the UK of a four times daily regimen. Even if there were to be a difference, more frequent dosing was likely to be more efficacious by providing more constant blood levels. Again, Zeneca contended that its claim for equivalence was based on comparison with a buserelin regimen which was at least as efficacious as the data sheet regimen.

Zeneca stated that the Tapanainen study was a key element in the application for a Zoladex product licence for this indication. The expert reviewers at the UK and other national regulatory authorities clearly considered that it was an adequate study to demonstrate the efficacy of Zoladex using buserelin as the reference. If they had considered Zoladex to be less effective, the product licence would not have been granted.

Zeneca concluded that the buserelin dosage regimen in the Tapanainen study, taking total daily dose and frequency into account, would be at least as efficacious, and possibly more efficacious than that outlined in the buserelin data sheet. It could not therefore be misleading to claim that Zoladex was as efficacious as buserelin, since the data probably, if anything, underestimated the relative efficacy of Zoladex compared with buserelin had it been used in exactly the manner outlined in the data sheet.

The company gave a brief overview on the role of buserelin and Zoladex in assisted conception.

APPEAL BOARD RULING

The Appeal Board noted that in assisted conception, Zoladex or buserelin were administered in order to achieve pituitary down-regulation. The Appeal Board noted Zeneca's submission that pituitary down-regulation was an all or nothing state and had to be achieved before a woman could enter the next phase of treatment. The Appeal Board noted from the Suprecur (buserelin) data sheet that to achieve pituitary down-regulation a total daily dose of 600 micrograms should be given although some patients might require a total daily dose of 1200 micrograms. The Appeal Board noted that although Tapanainen *et al* had used a buserelin dose of 1200 micrograms in all women this would minimize the risk of treatment failure in the small proportion of women who would not respond to 600 micrograms daily. Zoladex had thus been compared with the maximum licensed dose of buserelin. The study showed that the products were

equally effective in suppressing pituitary gonadotrophin secretion. The Appeal Board considered, therefore, that it was not misleading to claim that Zoladex was as effective as buserelin and no breach of Clause 7.2 was ruled.

The appeal on this point was successful.

2 Comparison of side effect profiles

COMPLAINT

Shire stated that the claims for a significantly better side effect profile for goserelin versus buserelin by Tapanainen *et al* were based on a questionnaire with a subjective estimation scale of the quality of a limited number of different complaints completed by patients post therapy. This was not a validated methodology to compare GnRH (gonadotrophin releasing hormone) agonist therapy to evaluate side effect profiles. One obvious omission was there was no mention of the number of completed questionnaires received by patients from each treatment group.

Shire was concerned about the use of this small study in promotional copy and considered the advertisement to be inaccurate and misleading as to any possible differences between goserelin and buserelin for UK clinicians and consequently damaging to the reputation of Suprecur Nasal Spray and Suprecur Injection. The dosage regimen quoted for intranasal buserelin was not the same as the licensed UK regimen, Suprecur Nasal Spray, and there were major flaws in extrapolating the patient subjective estimation scale questionnaires into the copy in the advertisement. For instance, as questionnaires were completed after oocyte recovery could the results have incorporated a bias in that was there a higher percentage of goserelin patients with a positive pregnancy test who submitted a questionnaire versus buserelin and would be more positive in their views on their therapy? This was not stated.

Shire stated that the questionnaire was not a validated methodology for comparing side effects/adverse event profiles in IVF. It was flawed as presented in the Tapanainen paper for several reasons. One obvious omission was the lack of numbers of completed questionnaires stated for each treatment group at each time point. Second the subjective side effects incorporated into the questionnaire were selected by the investigators and the basis for selection was not given. A number of side effects identified in the prescribing information were not included in the questionnaire and there was no open invitation for the patients to report all side effects. The patients were not asked, for example, about bruising at the site of administration, or arthralgia. Third the results for the side effects, irritability, nausea and swelling were not given numerically and only described in the paper in Figures 1 and 2 for the remainder. Nausea was not mentioned in the prescribing notes so it would be interesting to see the numerical results. Use of the symptom "depression" was highly questionable in the paper since this term medically usually referred to a clinical diagnosis. Shire noted that Zeneca had selectively not included this term in its advertisement. Fourth, it was not clear in Figures 1 and 2 in the paper precisely when the first set of questionnaires were completed in relation to therapy. If they were completed immediately prior to starting therapy, then there was already a treatment bias between the two groups at baseline. Finally, the last sentence of the first paragraph of the discussion in the paper made a generalisation about side effects from very limited selected data that Shire found unacceptable.

RESPONSE

Zeneca stated that in correspondence with the company Shire had raised the matter of the questionnaire used by Tapanainen *et al* and suggested there was bias because there might have been a higher percentage of goserelin patients with a positive pregnancy test who submitted a questionnaire compared with the buserelin group and consequently would have been more positive in their views on their therapy. Zeneca had replied that there could not have been any bias since the questionnaire was conducted before any pregnancy tests were performed. The company was surprised to see Shire reiterating verbatim the same allegation and making no reference to Zeneca's response.

Zeneca noted that Shire contended that the Tapanainen study was flawed in a number of respects and its criticisms were centred largely on the lack of some elements of information in the published paper. In addition Zeneca noted that Shire also criticised the authors' use of the term "depression" as a side effect and then appeared to be critical of Zeneca for not having made the promotional claim that there was significantly less depression associated with goserelin compared with buserelin. Zeneca did not consider that it was its position to defend the style or manner in which authors presented their study results in a publication. However, the company did accept that it had a responsibility to take reasonable steps to ensure that any study which it used in a promotional context was scientifically sound and represented the balance of the evidence. Zeneca considered this was the case for the study by Tapanainen *et al* . The paper was published in Human Reproduction which was one of the most respected journals in this field of medicine. Before being accepted for publication in this journal, papers were sent to external referees and were also reviewed by the editorial board of the journal. Human Reproduction had confirmed that this procedure was followed for the paper by Tapanainen *et al*. Furthermore, the Tapanainen study formed part of the company's MAA to the UK Licensing Authority and Zeneca had received no criticisms of the study from the Medicines Control Agency (MCA). The company could not agree with Shire that the methodology of this study was flawed. In an attempt to resolve the matter, Zeneca had sought an independent expert opinion. The company had shown the relevant correspondence of this case to the author of the expert report submitted to the MCA as part of Zeneca's MAA. His written opinion was provided. Both Zeneca and Shire were agreed that the Tapanainen study was the only direct comparison of goserelin with intranasal buserelin for pituitary down-regulation in this indication. For this and the above reasons, Zeneca considered that it was perfectly legitimate to use the Tapanainen study in promotional material.

PANEL RULING

The Panel noted the concerns about the questionnaire. The Panel considered that an assessment of side effects by the patient was necessarily subjective. This did not in itself negate the value of the data.

The Panel noted that the claim in the advertisement relating to the comparative incidence of side effects was that with Zoladex "Significantly less tiredness, headache and abdominal pain were reported in the first 2 to 3 weeks of treatment when compared to intranasal buserelin". In the discussion section of the Tapanainen paper the authors reported that the increased incidence of these side-effects might have been due to the fact that many patients found the administration of intranasal spray several times a day inconvenient. The Panel noted that the total daily dose of buserelin had been given in six divided doses and not in four divided doses as recommended in the UK data sheet. The Panel referred to its comments in point 1 above and considered that with regard to the licensed dosage frequency of intranasal buserelin the comparative claim relating to side-effects was misleading and unfair. A breach of Clause 7.2 was ruled.

APPEAL BY ZENECA PHARMA

Zeneca noted the complex and convoluted arguments put forward by Shire in support of this complaint. By mixing up arguments relating to efficacy with those relating to side effects, Shire had made it difficult to answer its points in a clear and logical way, and for the Panel to make a ruling. Zeneca considered that in satisfactorily answering the efficacy comparison complaint this also satisfactorily answered most, if not all, of the side effects comparison complaint. The company understood from the Panel's ruling that it had not accepted Shire's various arguments in relation to side effects except the one relating to the dosage frequency and level being different in the Tapanainen study from the UK data sheet.

With regard to the total daily dose, Zeneca stated that a comparison of side effects was only fair and not misleading if it was made at a buserelin dosage level which provided equivalent efficacy (ie 1200 micrograms) to Zoladex and this was done in the Tapanainen study. A lower total buserelin dose might of course have had fewer side effects (although Zeneca was not aware of any evidence for this) but that would be a misleading comparison because, as stated in the Shire data sheet, not all patients responded at the lower dose.

With regard to dosage frequency, Zeneca understood that Shire had not stated that there was any evidence that buserelin dosage frequency affected side effect incidence and Zeneca was not aware of studies comparing four and six times daily buserelin regimens at the same total daily dose.

Zeneca noted that the Panel drew attention to the comments in the Tapanainen paper, "many patients found the administration of intranasal buserelin spray several times a day to be inconvenient" and "the difference in side effects observed between the two patient groups was due to the different mode of administration". However, the Panel appeared to have misunderstood the significance of the comments. The author was not making any judgement that six times a day was worse then four times a day. Rather the comments were comparing multiple daily buserelin nasal applications with one long acting depot injection of Zoladex which lasted 28 days.

Zeneca added that there was no pharmacological reason to suggest that the side effects profile seen with four times daily buserelin should be less than six times daily dosage. In fact the opposite could be true. Higher peak blood levels associated with giving the same total daily dose in bigger doses less frequently as in the data sheet could increase the incidence of any side effects related to blood levels.

Zeneca concluded that comparing side effects between treatments used for oestradiol down regulation was not misleading when the daily doses had equivalent efficacy and within the licensed total daily dose ie buserelin 1200 micrograms daily and Zoladex depot injection. Also the buserelin dosage frequency in the study would, if anything, have produced a lower incidence of side effects than the dosage frequency recommended in the UK data sheet. The comparison of side effects was therefore fair and objective and was not misleading.

The company stated that the pharmacological basis of tiredness and abdominal pain as side effects of buserelin was unknown. Headache was thought to originate from the act of sniffing an alcohol based product. On that basis both the route of administration and the frequency of buserelin dosage might be related to the incidence of headache.

APPEAL BOARD RULING

The Appeal Board noted from its ruling in point 1 that all women had been treated with the maximum licensed dose of buserelin (1200 micrograms daily) in order to minimize the risk of treatment failures. Most women would have needed only half this dose of buserelin to achieve pituitary down-regulation and had thus received too much buserelin for the required clinical outcome. The Appeal Board noted that Zeneca had not produced any information to show that buserelin dosed at 200 micrograms six times daily did not produce any more side effects than buserelin dosed at 150 micrograms four times daily, the dose which would have worked in most women. The Appeal Board noted the view that the incidence of headache was possibly related to dosage and frequency of administration of buserelin nasal spray. The Appeal Board considered that given the high dose and frequency of buserelin the comparative claim regarding side-effects was misleading and the Panel's ruling of a breach of Clause 7.2 was upheld.

The appeal on this point was unsuccessful.

Complaint received **1 September 1998**

Case completed **14 January 1999**

CASE AUTH/764/9/98

LILLY v SMITHKLINE BEECHAM

Seroxat exhibition stand

Lilly alleged that an exhibition stand for Seroxat (paroxetine) used by SmithKline Beecham at an international meeting held in the UK was misleading as it gave the impression that Seroxat was indicated as a treatment for social phobia.

The Panel noted that the exhibition stand displayed material not only relating to those uses of Seroxat as detailed in the UK summary of product characteristics but also some material relating to social anxiety/social phobia which was not at the time of the meeting an indication licensed in the UK. It was a licensed indication in Romania. Three exhibition panels were headed Social Anxiety Disorder/Social Phobia. Although these exhibition panels did not mention the product name they were indistinguishable in style from the other exhibition panels and appeared beneath Seroxat banners which hung over the whole of the stand. A footnote on the three exhibition panels referred the reader to prescribing information. The Panel considered that the layout and content of the exhibition panels meant that they formed an integral part of the promotional stand and were thus promotional for Seroxat. The Panel considered that the exhibition panels failed to include a clear and prominent statement that paroxetine was not licensed in the UK for the treatment of social phobia and accordingly a breach of the Code was ruled.

COMPLAINT

Eli Lilly and Company submitted a complaint about an exhibition stand for Seroxat (paroxetine) used by SmithKline Beecham Pharmaceuticals at an international meeting held in the UK. Lilly alleged that the exhibition stand was misleading and gave a clear impression that paroxetine was indicated as a treatment for social phobia, which it clearly was not. This was done by using a type of Venn diagram which interlinked disease areas, namely depression, obsessive compulsive disorder (OCD), panic and social phobia, which was featured throughout the promotional section of the stand. There was also an image of two stylised faces turned towards each other with the slogan "Two problems One solution" which recurred across exhibition panels on the stand which referred to both licensed and unlicensed indications (specifically social phobia).

Lilly stated that at the meeting a member of the organizing committee, who had attempted to negotiate on behalf of the company, had also interpreted the information in the same light and had communicated this to SmithKline Beecham.

Lilly alleged that the stand was in breach of Clauses 3 and 7 of the Code. Photographs were provided.

RESPONSE

SmithKline Beecham confirmed that the meeting in question was the Collegium Internationale Neuro Psychopharmacologicum (CINP) held in Glasgow, 13-16 July 1998 inclusive. It was the largest international psychiatry meeting in the calendar, and although on British soil this year, was attended by a full international audience.

Seroxat was licensed for social phobia in Romania on 26 June 1998 and on 21 September 1998 in the UK.

Notwithstanding the licence situation, SmithKline Beecham did not believe the exhibition panels in question were promotional. Two exhibition panels specifically described social phobia/social anxiety disorder, at no point was Seroxat or paroxetine mentioned.

SmithKline Beecham submitted that the exhibition panels were purely educational in nature, promoting awareness of this condition, and access to a non-product specific SmithKline Beecham social phobia website.

At no point did any of the exhibition panels suggest that Seroxat was indicated for social phobia/social anxiety disorder, indeed the only exhibition panel which described Seroxat indications did so for depression and anxiety related disorders and specified only panic and OCD.

SmithKline Beecham confirmed that the reason social phobia was included in the Venn diagram was because this completed the spectrum of anxiety disorder and so completed the educational message of these exhibition panels. It should be stressed that on both exhibition panels which fully described the conditions of social phobia-social anxiety disorder, Seroxat/paroxetine was not mentioned and there was no implication of a licence for this indication.

SmithKline Beecham referred to the image of two stylised faces turned towards each other with the slogan "Two problems One solution". It did not refer to both licensed and unlicensed indications but instead referred to the two linked conditions of depression and anxiety and had been used for some time, well in advance of any discussion of social phobia. Seroxat was indicated for depression and depression with associated anxiety and also for the anxiety conditions of panic and OCD.

SmithKline Beecham stated that at no point were any claims made regarding Seroxat in social phobia/social disorder. All materials relating to this disorder were purely educational and non-product specific. SmithKline Beecham strongly refuted the allegation of a breach of Clause 7 of the Code.

SmithKline Beecham noted that Lilly alleged that a member of the organizing committee had also interpreted the information in the same light. This was not correct. Lilly went to the organizers before approaching SmithKline Beecham. The committee member had tried to act as a mediator but had fully accepted the company's view and was concerned that he had been drawn into an

inter-company discussion. SmithKline Beecham considered that Lilly's action in this regard brought the industry into disrepute.

SmithKline Beecham did not believe that it had promoted Seroxat for the indication of social phobia. It believed its materials were balanced, not misleading and not in breach of Clauses 3 or 7.

SmithKline Beecham provided copies of all the exhibition panels together with a detailed plan of the stand.

PANEL RULING

The Panel noted that the summary of product characteristics for Seroxat stated that it was indicated for the treatment of depressive illness of all types including depression accompanied by anxiety, obsessive compulsive disorder and panic disorder.

The Panel noted that the CINP was an international meeting held in the UK. At the time the meeting was held Seroxat was licensed for social phobia in Romania but not in the UK.

The Panel noted from the plan of the stand provided that exhibition panels were displayed in four areas according to clinical condition. Exhibition panels 1 to 5 dealt with the use of Seroxat in panic and on the reverse panels 6 to 8 dealt with the product's use in OCD. Exhibition panels 12 to 16 detailed the use of Seroxat in depression while on the reverse panels 9 to 11 dealt with social anxiety/social phobia. The plan showed a banner hanging above both sets of exhibition panels and from the photographs provided the Panel noted that the banners were printed with Seroxat in logo type together with the image of two stylised faces turned towards each other.

The Panel examined the exhibition panels. A Venn diagram which illustrated the relative incidence of major depression and its associated conditions of obsessive compulsive disorder, panic disorder and social phobia appeared on several of the exhibition panels beneath the sub-heading 'The Problem'. The exhibition panels discussed Seroxat and *inter alia* the treatment of panic disorder, obsessive compulsive disorder and depression. Exhibition panels 9 to 11 were headed Social Anxiety Disorder/Social Phobia and discussed this condition and stated the need for greater public recognition, earlier diagnosis, effective treatment and confirmed SmithKline Beecham's commitment to raise public awareness and increase understanding. Exhibition panel number 11 referred delegates to the company website on social anxiety disorder and social phobia. Whilst these three exhibition panels did not mention Seroxat they were of the same design format as the other exhibition panels and were placed beneath Seroxat banners. The Panel noted that a footnote to each exhibition panel referred the reader to a SmithKline Beecham representative at the exhibition for prescribing information. In the opinion of the Panel the layout style and content of the exhibition panels in question meant that they formed an integral part of the promotional stand and were thus promotional for Seroxat.

The Panel noted the requirements of Clause 3 of the Code together with the supplementary information headed "Promotion at international conferences". The supplementary information stated that the display and provision of promotional material for medicines or indications for medicines which did not have a marketing authorization in the UK but were so authorized elsewhere was permitted at international meetings in the UK provided that any promotional material for medicines or for indications which did not have a UK marketing authorization were clearly and prominently labelled as such. The meeting had to be a truly international meeting of high scientific standing with a significant proportion of the delegates from outside the UK and the promotional material had to be certified in accordance with Clause 14 of the Code except that the signatories need to certify only that in their belief the material was a fair and truthful presentation of the facts about the medicine. The Panel also noted that at the date of the conference, 13 to 16 July 1998, although so licensed in Romania, Seroxat did not have a licence in the UK for the treatment of social phobia and exhibition panels 9-11 did not include a statement to this effect.

The Panel noted from the plan of the stand that there were two interactive desks each with two computer terminals. From exhibition panels mounted behind the terminals the Panel noted that the company website for social anxiety and social phobia included a library, consulting rooms which provided case histories and diagnostic criteria and finally meeting reports. A footnote in small type face to the guidance regarding use of the website stated that "Paroxetine is not currently indicated in the UK for the treatment of social anxiety disorder/social phobia."

The Panel noted that the information provided about social phobia on exhibition panels 9-11 did not include a statement to the effect that Seroxat was not licensed for that indication in the UK. In the Panel's opinion the statement to that effect which appeared on the exhibition panels by the computer terminals was not sufficiently prominent. The Panel considered that both sets of exhibition panels had failed to meet one of the conditions in the supplementary information. A breach of Clause 3.2 of the Code was ruled. The Panel considered that the allegation of a breach of Clause 7.2 of the Code was covered by this ruling.

During its consideration of this case, the Panel noted that exhibition panel 19 stated "Enter our daily quiz win a T-shirt." The supplementary information to Clause 18.2 of the Code referred to competitions and quizzes. Competitions had to be a *bona fide* test of skill and recognise the professional standing of the recipients. The supplementary information referred to the cost of competition prizes. In addition prizes had to be relevant to the potential recipient's profession or employment. The Panel queried the relevance of a T-shirt and decided that the competition should be taken up with SmithKline Beecham under the provisions of Paragraph 16 of the Constitution and Procedure.

Complaint received **14 September 1998**

Case completed **30 November 1998**

PRESCRIBING UNIT MANAGER v SCHERING-PLOUGH

Detrunorm journal advertisement

A prescribing unit manager alleged that a journal advertisement for Detrunorm (propiverine) issued by Schering-Plough was in very poor taste and inappropriately derived humour from a common and debilitating condition. The advertisement featured a photograph of an elderly woman looking up at a pair of knickers hanging on a washing line. The headline was "I only wet them when I wash them".

The Panel accepted that some people might be offended by the advertisement but considered that this would not be a view shared by the majority of the audience. No breach of the Code was ruled.

A prescribing unit manager complained about an advertisement for Detrunorm (propiverine) (ref DT98/002) issued by Schering-Plough Ltd which appeared in The Pharmaceutical Journal, 12 September 1998. The advertisement featured a photograph of an elderly woman looking up at a pair of knickers hanging on a washing line. The headline was "I only wet them...when I wash them."

According to the summary of product characteristics (SPC) Detrunorm had been shown to be efficacious in those patients who had either idiopathic bladder instability, or neurogenic bladder (detrusor hyperreflexia) from spinal cord injuries eg transverse lesion paraplegia for: urinary incontinence, urgency and frequency in unstable bladder conditions.

COMPLAINT

The complainant alleged that the advertisement was in very poor taste and inappropriately derived humour from a common and debilitating condition.

RESPONSE

Schering-Plough did not consider the advertisement to be in poor taste, nor in breach of the Code. To the contrary it believed the advertisement to be sympathetic to the distress which could be caused by the disease, as well as the problems faced by healthcare professionals in treating patients.

Prior to completion and distribution of the Detrunorm advertisement, Schering-Plough had consulted widely amongst healthcare professionals and patients to ensure the advertisement was sympathetic to this debilitating condition. When shown the Detrunorm advertisements healthcare professionals reacted extremely positively towards it and were not offended by the headline or the image. Further questioning showed that this was because the woman in the advertisement was not the target of the humour, but the origin of it - the joke was from her, not on her. It was this "patient empowering" aspect of the advertisement that made it appealing.

Schering-Plough referred to endorsements of the Detrunorm advertisement from healthcare professionals whose job it was to manage urinary incontinence. Three patient interest groups expressed the view that this advertisement was not offensive and/or were positive to the tone and content of the advertisement.

Schering-Plough submitted that the Detrunorm advertisement did not disparage or belittle the patient, disparage competitors or their products, trivialise the condition, employ naked figures or other forms of titillation, or criticise or undermine the role of the GP.

Schering-Plough believed the Detrunorm advertisement was sympathetic to the distress of urinary incontinence and could not reasonably be judged to be in poor taste, given the level of support for the advertisement from patient and healthcare professional bodies responsible for the daily care of patients with this disease.

PANEL RULING

The Panel noted that matters of humour and taste were subjective. The Panel accepted that some people might be offended by the advertisement but considered that this would not be a view shared by the majority of the audience. The Panel considered that the advertisement was not unacceptable in relation to the requirements of Clause 9.1 of the Code and no breach was ruled.

Complaint received **18 September 1998**

Case completed **26 November 1998**

CASE AUTH/766/9/98

PHARMACIA & UPJOHN v SCHERING-PLOUGH

Promotion of Detrunorm

Pharmacia & Upjohn complained about an abbreviated advertisement, a full journal advertisement and a launch mailing issued by Schering-Plough in relation to its product Detrunorm (propiverine).

The claim "I only wet them when I wash them" appeared on all three items in association with a photograph of an elderly lady looking up at a pair of knickers hanging on a washing line. Pharmacia & Upjohn alleged that this was an exaggerated claim because it implied that Detrunorm would lead to a completely dry patient. Clinical trials, although showing a significant improvement in urinary incontinence, resulted in only a small reduction in incontinence episodes and only some patients actually being dry. The Panel considered that the photograph and claim created the impression that treatment with Detrunorm would result in all incontinence patients being completely dry all of the time but according to the data this was not so. The impression created was exaggerated and a breach of the Code was ruled.

The claim "new for urinary incontinence" appeared in all three items. The claim "New Detrunorm handles urinary incontinence with care" and "Detrunorm is a new treatment for bladder instability" appeared in the mailing. Pharmacia & Upjohn alleged that Detrunorm was being promoted for urinary incontinence without qualification whereas it was actually licensed only for use in patients who had detrusor instability or detrusor hyperreflexia and not for other types of urinary incontinence. The Panel considered that the first impression from all three items was that Detrunorm was licensed for use in all types of urinary incontinence which was not so. The claims were misleading and each of the three items was ruled in breach of the Code.

Pharmacia & Upjohn Ltd complained about the promotion of Detrunorm (propiverine) by Schering-Plough Ltd. The materials at issue were an abbreviated advertisement which had appeared in MIMS, September 1998, a full advertisement which had appeared in Pulse, 12 September 1998 (ref DT98/002), and a launch mailing (ref DT98/007).

Detrunorm was indicated for use in adults, who had either idiopathic bladder instability or neurogenic bladder from spinal cord injuries, for urinary incontinence and urgency and frequency in unstable bladder conditions. Pharmacia & Upjohn marketed Cystrin (oxybutynin) for similar indications and in addition the product could also be used for nocturnal enuresis in children over five years of age in certain situations.

1 Claim "I only wet them when I wash them"

This claim featured in all three pieces of promotional material. In each case the claim was associated with a photograph of an elderly lady looking up at a pair of knickers hanging on the washing line.

COMPLAINT

Pharmacia & Upjohn alleged that the claim was in breach of Clause 7.8 of the Code which stated that exaggerated or all-embracing claims must not be made and superlatives must not be used except for those limited circumstances where they related to a clear fact about a medicine.

Pharmacia & Upjohn alleged that the claim implied that treatment with Detrunorm would lead to a completely dry patient. The clinical trials, however, although showing a significant improvement in urinary incontinence, resulted in only a small reduction in incontinence episodes, and only some patients actually being dry. This was confirmed by Schering-Plough in intercompany correspondence where it was stated that only some patients who took Detrunorm would become completely dry. Pharmacia & Upjohn referred to Homma *et al* (1997) which showed reductions in urinary incontinence of 1.2 times per 24 hours and Okada *et al* (1998) which showed only subjective improvements in urge incontinence, with 64.5% of patients reporting excellent improvement, 32.5% reporting moderate improvement, and 3.2% reporting poor improvement.

Pharmacia & Upjohn stated that it was therefore clear that in leading physicians to believe that treatment with Detrunorm would lead to a completely dry patient, Schering-Plough was making an exaggerated claim in breach of Clause 7.8 of the Code.

RESPONSE

Schering-Plough stated that this claim, in common with many pharmaceutical advertisements, showed a resolution to a very common problem. It depicted a lady saying "I only wet them when I wash them" implying, on this occasion, that she had a positive outcome and no longer wet her underwear. It differed very little from other advertising depicting a happy patient with an example of their condition improving. Schering-Plough gave three examples of such advertising.

Schering-Plough stated the advertisement was designed to show a positive outcome to therapy and not an all encompassing statement of efficacy of dryness in every patient.

PANEL RULING

The Panel considered that the photograph and claim created the impression that treatment with Detrunorm would result in all incontinent patients being completely dry all of the time. According to data this was not so. The abstract by Homma *et al* gave the results of a study comparing the clinical efficacy of temiverine and propiverine for unstable bladder and detrusor hyperreflexia. Eighty seven patients were treated with propiverine, 40.2% of which were judged to have had an

excellent or good response. The majority of patients thus had no better than a fair response. Individual symptoms were significantly improved after treatment in both groups. The paper by Okada *et al* (1998) reported a study assessing the clinical effect of propiverine in patients with urge or stress incontinence. Although the results were favourable, with propiverine reducing urinary urgency, incontinence and limitations in daily activities in over 91% of patients, the Panel did not consider that stress incontinence was within the Detrunorm licence. (see point 2)

The Panel considered that, given the data, the impression created by the photograph and the claim in all three pieces of promotional material, the abbreviated advertisement, the full advertisement and the launch mailing, was exaggerated and ruled a breach of Clause 7.8 of the Code.

2 Claims "new for urinary incontinence" "New Detrunorm handles urinary incontinence with care" "A fresh approach in the treatment of urinary incontinence"

The claim "new for urinary incontinence" appeared above the product logo in all three promotional items at issue. The abbreviated advertisement consisted of two elements, the claim "I only wet them when I wash them" and its associated visual and the product logo. The full advertisement was similar to the abbreviated advertisement but also featured a claim comparing the efficacy and tolerability of Detrunorm with that of oxybutynin.

The claim "New Detrunorm handles urinary incontinence with care" appeared on page 2 of the mailer as a heading to a two page spread of the elderly lady looking up at the washing line. Page three flapped out leaving page 2 in view but in addition revealing two other pages detailing clinical data comparing Detrunorm and oxybutynin and text that began "Detrunorm is a new treatment for bladder instability". The prescribing information appeared on the bottom of the opened right hand flap.

The claim "A fresh approach in the treatment of urinary incontinence" appeared as a heading to the back page of the mailer.

COMPLAINT

Pharmacia & Upjohn alleged that the claims were in breach of Clauses 3.2, 7.2 and 7.8 of the Code.

Pharmacia & Upjohn stated that Detrunorm was being advertised as "new for urinary incontinence" whereas careful reading of the summary of product characteristics (SPC) revealed that the product was actually licensed for the treatment of urinary incontinence, or urinary urgency and frequency, only in patients who had detrusor instability or detrusor hyperreflexia. Detrunorm was not licensed for treatment of any other type of urinary incontinence, eg stress incontinence, and this had been confirmed in intercompany correspondence. Pharmacia & Upjohn alleged a breach of Clause 3.2 as the promotional material indicated that Detrunorm was licensed for treatment of urinary incontinence without any qualifications as to which types of urinary incontinence, ie the material implied all incontinence, including stress incontinence, fistulae etc.

Pharmacia & Upjohn stated that in addition, these advertisements might lead the physician to believe that Detrunorm could be used for treatment of all types of urinary incontinence as there was no indication of the types of incontinence for which Detrunorm was licensed in the advertisements. Pharmacia & Upjohn noted that in intercompany correspondence Schering-Plough had agreed that the statement "new for urinary incontinence" could be ambiguous. Pharmacia & Upjohn alleged that these claims were in breach of Clause 7.2.

Pharmacia & Upjohn considered that the statements were all embracing for urinary incontinence, whereas Detrunorm was only licensed for the treatment of urinary incontinence as a result of bladder instability or neurogenic bladder. The company alleged a breach of Clause 7.8.

RESPONSE

Schering-Plough confirmed that it had agreed to amend the claim "new for urinary incontinence". It was its intention to include an asterisked statement, qualifying the claim, stating bladder instability and detrusor hyperreflexia. This statement was already present and clearly legible on the main advertising in the prescribing information.

The other statement on the full advertisement referred to oxybutynin which was generally well known as an agent for detrusor instability.

Schering-Plough noted that the claims "New Detrunorm handles urinary incontinence with care" and "A fresh approach in the treatment of urinary incontinence" appeared in the context of a launch mailing. The front page resembled a washing machine. On the inside pages written information was introduced with the words "Detrunorm is a new treatment for bladder instability". The material also included prescribing information where the indications for this product were clearly printed. A clinical trial was outlined comparing Detrunorm and oxybutynin, looking at improvement in urgency - an indication commensurate with the SPC. Again, oxybutynin was a well known agent for the treatment of bladder instability.

Schering-Plough provided copies of an older advertisement for oxybutynin [not the Pharmacia & Upjohn brand of the medicine] where "Urinary incontinence" was in a very prevalent position. Oxybutynin's indications differed only slightly to Detrunorm with the inclusion of nocturnal enuresis. Schering-Plough was unaware of any complaint against this advertisement on the grounds that the indication in the headline was unqualified and on this basis it believed the statements referred to in the Detrunorm mailing were clear, unambiguous and consistent with the SPC. It, therefore, did not consider that Clauses 3.2, 7.2 or 7.8 had been breached.

PANEL RULING

The Panel noted that the SPC for Detrunorm stated that it was indicated for those patients who had either idiopathic bladder instability, or neurogenic bladder (detrusor hyperreflexia) from spinal cord injuries, eg transverse lesion paraplegia, for urinary incontinence, urgency and frequency in unstable bladder conditions. The Panel considered that the wording of the SPC was such as to qualify which types of urinary incontinence were licensed indications. Detrunorm was not licensed to treat all types of urinary incontinence.

The Panel considered that the claims "new for urinary incontinence", "New Detrunorm handles urinary incontinence with care" and "A fresh approach to the treatment of urinary incontinence" gave the impression that Detrunorm was indicated for all forms of urinary incontinence.

The Panel noted that the abbreviated advertisement made no mention of either bladder instability or neurogenic bladder from spinal cord injuries. The full advertisement included the prescribing information which gave details of the licensed indications for Detrunorm. The mailer also contained the prescribing information and in addition text which began "Detrunorm is a new treatment for bladder instability". The Panel considered that, despite the inclusion of prescribing information on the full advertisement and the mailer and the layout of qualifying text in the mailer, the first impression from all three pieces was that Detrunorm was licensed for use in all types of urinary incontinence which was not so. The Panel did not accept Schering-Plough's implied submission that reference to oxybutynin would by implication define Detrunorm's licensed use. The Panel ruled that the three claims were misleading and the three pieces of promotional material were each in breach of Clause 7.2 of the Code. The Panel considered that the allegations of a breach of Clauses 7.8 and 3.2 were covered by this ruling.

During its consideration of this matter the Panel noted Schering-Plough's intention to asterisk claims regarding urinary incontinence and to refer to bladder instability and detrusor hyperreflexia. The Panel considered that this was not necessarily unacceptable but noted that that the qualifying text should be easily read and in the same visual field as the term "urinary incontinence". The Panel requested that Schering-Plough be advised of its views in this matter.

Complaint received **21 September 1998**

Case completed **14 December 1998**

CASE AUTH/767/9/98

GENERAL PRACTITIONER v SCHWARZ PHARMA

Viridal Duo "Dear Doctor" letter

A general practitioner complained about the front page of a "Dear Doctor" letter sent by Schwarz Pharma in relation to Viridal Duo which made no mention of the non-proprietary name, alprostadil, although the brand name appeared five times.

The Panel noted that the most prominent display of the brand name was in logo type as a heading to the letter. The only reference to alprostadil was in the prescribing information printed on the back. The Panel ruled a breach of the Code as the company had failed to include the non-proprietary name immediately adjacent to the most prominent display of the brand name.

A general practitioner complained about a Viridal Duo (alprostadil) "Dear Doctor" letter which had been sent by Schwarz Pharma Limited. The A4 letter was prominently headed with Viridal Duo in logo type and gave details regarding the use of the product.

COMPLAINT

The complainant noted that the front page of the letter made no mention of the approved name although the brand name appeared five times. The complainant understood that there was a requirement in advertising and mailings etc that the approved name should be displayed in close proximity to the brand name and questioned whether or not the letter was in breach of the Code.

RESPONSE

Schwarz pointed out that the copy of the "Dear Doctor" letter sent to the Authority was a photocopy and of one side only, hence the prescribing information was not included. However, the letter did have the prescribing information printed on the reverse and thus the company did not perceive any breach of Clause 4.1 as suggested.

Schwarz did not consider that it was in breach of any other clause of the Code. However, to avoid confusion in the future, the next time the letterhead was printed, it would include mention of the approved name, next to 'Viridal Duo', on the front side of the paper.

PANEL RULING

The Panel noted that the complainant had provided the Authority with an original copy of the "Dear Doctor" letter which had in turn been photocopied and sent to Schwarz when the company was notified of the complaint. The original letter from the complainant had included prescribing information on the reverse. The letter thus complied with the Code in that regard.

The Panel noted that the "Dear Doctor" letter contained several references to Viridal Duo and that the brand name appeared in logo type as a heading. The only reference to

alprostadil, the non-proprietary name, was in the prescribing information printed on the back of the letter. The Panel noted that Clause 4.2 of the Code listed the component parts of the prescribing information and, in addition, stated that the non-proprietary name or a list of active ingredients must appear immediately adjacent to the most prominent display of the brand name in not less than 10 point bold or in a type size which occupied a total area no less than that taken by the brand name. Clause 4.1 of the Code stated that the information listed in Clause 4.2 must be provided. Failure to do so would therefore be a breach of this Clause and not of Clause 4.2.

The failure to include the non-proprietary name immediately adjacent to the most prominent display of the brand name, which in the Panel's view was the letter heading, meant that Schwarz had not complied with Clause 4.1. The Panel therefore ruled a breach of Clause 4.1 of the Code.

Complaint received **22 September 1998**

Case completed **26 October 1998**

CASE AUTH/768/9/98

PHARMACIA & UPJOHN v ALLERGAN

Patient poster

Pharmacia & Upjohn alleged that a poster aimed at patients with glaucoma distributed by Allergan advertised a prescription only medicine to the public. The brand name Alphagan appeared on the poster together with the product logo. The poster included information on glaucoma and its treatment. Pharmacia & Upjohn alleged that prescribing information should have been included.

Allergan stated that the poster was designed as an educational aid. The Panel noted that the poster provided useful general information for patients about the diagnosis and treatment of glaucoma.

The Panel ruled a breach of the Code as the inclusion of the product branding meant that it in effect promoted Alphagan (brimonidine tartrate ophthalmic solution 0.2%) which was a prescription only medicine. The poster when provided to healthcare professionals promoted Alphagan. The prescribing information should have been supplied. A breach of the Code was ruled in that regard. In the Panel's view the name of the medicine and the prescribing information should have been put on the back of the poster.

Pharmacia & Upjohn Limited complained about a patient poster designed for display in the surgery or clinic entitled "A Guide to the Treatment of Glaucoma" (ref 3015/0024/1) and distributed by Allergan Limited. The poster discussed the symptoms, causes, detection and treatment of glaucoma. Allergan's tradename, Alphagan, appeared prominently in logo type in the bottom right hand corner of the poster adjacent to the product logo. The non-proprietary name (brimonidine tartrate ophthalmic solution 0.2%) appeared beneath the brand name and immediately adjacent to the brand name was an inverted black triangle. Alphagan was marketed by Allergan for open angle glaucoma.

COMPLAINT

The poster had been used recently by the Allergan sales team and was still present in many ophthalmology out-patient departments. Pharmacia & Upjohn alleged that the poster breached Clause 20.1 of the Code as it branded and named Alphagan on a poster aimed at the general education of patients regarding glaucoma and its treatment - including those patients not receiving Alphagan. Pharmacia & Upjohn had noted by particular reference to a section of the poster entitled "How to use eye drops" that the language of the poster was specifically aimed at patients ie "Hold down the corner of your eyelid....". Indeed, the aim of the poster (ie patient education) had been acknowledged by Allergan in correspondence between the companies and, therefore, Pharmacia & Upjohn considered that the breach of Clause 20.1 could not be in any doubt.

Pharmacia & Upjohn stated that, in addition, as the poster listed both the brand name and indication, it should bear prescribing information. As this was clearly lacking, this was a breach of Clause 4.1 of the Code..

RESPONSE

Allergan stated that the posters were part of a series of treatment guides which included information on a particular disease (in this case glaucoma) and its treatment. They were intended for use exclusively by doctors and other healthcare professionals during discussions with their patients about glaucoma.

Allergan submitted that Pharmacia & Upjohn had misinterpreted the intended use of the poster by picking up the point that the section designed to educate on the correct instillation of eye drops showed a patient putting in their own eye drops. There seemed little purpose in showing a doctor administering eye drops as in reality it was the patient who needed to learn this procedure for themselves. The language used in this section, referred to as "simplistic" by Pharmacia & Upjohn, was worded in such a way so as to enable the doctor to take the patient through this process in a manner that could be easily followed and understood. Allergan, therefore, did not consider that the patient poster constituted advertising to the general public and strongly denied a breach of Clause 20.1.

Allergan confirmed that the poster was designed as an educational aid. However, even if it was considered to be promotional because it carried the Alphagan trademark, it would not require prescribing information under the Code as it did not make any claims or provide any product information. Consequently there was no breach of Clause 4.1.

Allergan confirmed that this poster was no longer in distribution and had ceased being used some months ago.

PANEL RULING

The Panel noted that Clause 20.1 of the Code prohibited the advertising of prescription only medicines (POMs) and certain other medicines to the general public. Clause 20.2 of the Code permitted information to be made available to the public provided it was factual, balanced and did not raise unfounded hopes of successful treatment or mislead with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine.

The Panel noted that generally information to the public fell into one of two categories. Firstly, disease area information that was relevant to anybody with the disease regardless of their treatment. Such material could refer to treatments in general terms but should not favour one medicine over others as this would be viewed as promotion of that medicine. Secondly, product specific information which could only be provided to patients already prescribed the product. Provision of such material to patients not prescribed the medicine would be seen as advertising to the general public. Provision of product specific material to healthcare professionals to give to patients who had been prescribed the product constituted promotion of that product and prescribing information should be provided to the healthcare professionals separately from the material itself. It should not be included on the material for the patient.

The Panel noted that the poster was headed "A Guide to the Treatment of Glaucoma" and was intended to be used by doctors and other healthcare professionals to educate patients on their condition and would be used during discussions with patients. The section entitled "Treating Glaucoma" included a discussion of treatment with different medicines ie alpha2 agonists, miotics, beta blockers, adrenergic neurone blockers, carbonic anhydrase inhibitors and prostaglandins; no individual medicines were mentioned by name. Laser treatment and surgery were also mentioned.

The Panel noted Allergan's submission that the patient poster provided disease information and was supplied as an educational aid. The Panel considered that the poster did provide useful information for the patients about the diagnosis and treatment of glaucoma and would be used generally with patients suffering from glaucoma, not just with those prescribed Allergan's product.

The Panel noted that pharmaceutical companies had provided disease information posters for patients in the past. If such items were branded, then the branding information together with the prescribing information appeared on the reverse of the poster which would not be seen by the general public. This was in order to comply with the requirements for prescribing information given in Clause 4.1, and the prohibition on advertising POMs and certain other medicines to the public in Clause 20.1 of the Code. The back of such posters was often marked "not for display to the public" or similar.

The Panel considered that the poster in effect promoted Alphagan. It included the brand name Alphagan, which was a prescription only medicine.

The Panel ruled a breach of Clause 20.1 of the Code as the poster promoted a prescription only medicine to the general public. The Panel considered that the poster also promoted Alphagan to healthcare professionals and therefore prescribing information should have been supplied. A breach of Clause 4.1 of the Code was ruled. The name of the product, its non-proprietary name and the prescribing information, should all have gone on the back of the poster.

Complaint received **29 September 1998**

Case completed **2 December 1998**

PASTEUR MÉRIEUX MSD v SMITHKLINE BEECHAM

Promotion of Typherix

Pasteur Mérieux MSD alleged that the claim "Typherix offers first class efficacy" which appeared in a GP mailing and advertisement for Typherix produced by SmithKline Beecham was unsubstantiated, misleading and exaggerated.

The Panel noted that Typherix (Vi polysaccharide typhoid vaccine) had been licensed on the basis that in healthy volunteers immunogenicity data had shown bioequivalence with Typhim Vi, produced by Pasteur Mérieux MSD. The Panel noted that in the area of vaccines the use of the word efficacy did not necessarily relate to clinical efficacy.

The Panel did not accept that the advertisement implied a superiority for the SmithKline Beecham product compared with the Pasteur Mérieux MSD product in relation to efficacy as alleged and considered that the intended audience would not be misled by the claim. No breach of the Code was ruled.

Pasteur Mérieux MSD Ltd complained about the promotion of Typherix (Vi polysaccharide typhoid vaccine) by SmithKline Beecham Pharmaceuticals. The materials at issue were a leaflet (ref TY/LF/8/015/QD) included in a GP mailing and an advertisement (ref TY/AD/8/017DR) which was published in Doctor, 13 August 1998. Both the mailing and the advertisement announced the launch of Typherix and included the claim "Typherix offers first class efficacy"

COMPLAINT

Pasteur Mérieux MSD stated that the clinical development of vaccines included studies designed to prove safety, immunogenicity efficacy and effectiveness of the vaccine. However it was not unusual for vaccines to be licensed on the basis of safety and immunogenicity alone. The company stated that following the use of "Typherix offers first class efficacy" it requested supporting data from SmithKline Beecham. Pasteur Mérieux MSD was informed that there was no efficacy data for Typherix. It could therefore conclude that Typherix was licensed on the basis of safety and immunogenicity alone.

Pasteur Mérieux MSD stated that in the absence of efficacy data the assumption of efficacy was based on the antibody levels induced by the vaccine. This surrogate marker of efficacy was an arbitrarily predefined antibody titre. All individuals with antibody titres which fell above this predefined level were said to be immunoprotected. This was the data available for Typherix.

Pasteur Mérieux MSD stated that to establish true vaccine efficacy a study must be performed in an endemic environment. It was not acceptable, in the absence of this kind of efficacy data, to make claims about efficacy. The claims for Typherix were not supported by efficacy data.

Pasteur Mérieux MSD stated that its product, Typhim Vi, was the only other injectable polysaccharide typhoid vaccine available in the UK. The efficacy of Typhim Vi was supported by a number of efficacy studies performed in endemic environments and these showed that the product was 70% to 80% efficacious.

Pasteur Mérieux MSD suggested that "first class" related to something with an efficacy far greater than 80%, indeed it probably inferred an efficacy approaching 100%. SmithKline Beecham was thus inferring that Typherix had a superior efficacy to Typhim Vi. The potential dangers of overstating the efficacy of typhoid vaccination and thus ignoring other travel health advice was highlighted in the 1996 edition of the Department of Health book: 'Immunisation against Infectious Disease.' In relation to typhoid vaccination the Department of Health stated "the vaccines are not 100% effective and the importance in preventing infection of scrupulous attention to personal, food and water hygiene must still be emphasised to those travelling to endemic areas."

In summary, Pasteur Mérieux MSD stated that by claiming that Typherix offered first class efficacy SmithKline Beecham was making a number of unsubstantiable and misleading claims.

- It was claiming efficacy in the absence of any supporting data.
- It was inferring that Typherix was superior to Typhim Vi.
- It was misleading the medical profession as to the efficacy of injectable polysaccharide typhoid vaccines.
- By making unrealistic claims SmithKline Beecham was not only potentially damaging its credibility it was also engendering unrealistic expectations for the Pasteur Mérieux MSD typhoid vaccine.
- If Typhim Vi did not fulfil the unrealistic expectations set by Typherix then one could reasonably expect Pasteur Mérieux MSD's credibility to be damaged through no fault of its own.

Pasteur Mérieux MSD alleged that the claim "Typherix offers first class efficacy" was in breach of Clauses 7.2, 7.3 and 7.8 of the Code.

RESPONSE

SmithKline Beecham agreed that typhoid vaccines were not 100% effective. Within the context of typhoid vaccines, however, the company considered that Typherix did offer first class efficacy by which it meant comparable efficacy to the best in class. Immunogenicity data had demonstrated bioequivalence between Typherix and the Pasteur Mérieux MSD brand Typhim Vi and based on this data, SmithKline Beecham was given a licence. One would therefore anticipate protective efficacy in an endemic environment to be equivalent for both vaccines. As Pasteur Mérieux MSD stated this was of the order of

70-80% for Typhim Vi. The Department of Health's guidelines 'Immunisation against Infectious Disease' endorsed this figure of 70 -80% protection over at least three years for typhoid Vi polysaccharide antigen vaccine. The guidelines also stated that whole cell typhoid vaccine (no longer available in the UK) conferred around 70-80% protection which faded after one year, while oral typhoid vaccine (Ty 21a) appeared to produce similar efficacy to parenteral vaccines, although the length of protection might be less. A published review of Typhim Vi capsular polysaccharide vaccine cited protective efficacy figures of up to 75% for Typhim Vi, up to 66% for whole cell vaccine and up to 67% for oral typhoid vaccine.

On the basis of the above SmithKline Beecham did not, therefore, consider that healthcare professionals would have unrealistic expectations of the efficacy of Typherix. In addition, the materials in question made no reference to the efficacy of the Pasteur Mérieux MSD vaccine Typhim Vi. No comparisons were made and no inference of superiority of Typherix was intended.

In conclusion, SmithKline Beecham did not consider that the claim 'first class efficacy' was in breach of Clauses 7.2, 7.3 or 7.8 of the Code of Practice.

PANEL RULING

The Panel noted that there was a difference in the way vaccines were licensed compared to other medicines. Typherix had been licensed on the basis that in healthy volunteers, immunogenicity data had shown bioequivalence with Typhim Vi. The protective efficacy of the vaccine in an endemic area had not been demonstrated but was anticipated on the basis of the immunogenicity data.

The Panel did not accept that the phrase "first class efficacy" related to something with an efficacy greater than 80% as alleged by Pasteur Mérieux MSD. The efficacy figure for Typhim Vi was higher than for other agents. The Panel did not accept that the advertisement implied a superiority for the SmithKline Beecham product compared with the Pasteur Mérieux MSD product in relation to efficacy.

The Panel noted that traditionally material was assumed to refer to the clinical situation unless stated otherwise. The Panel considered that in the area of vaccines the use of the word efficacy did not necessarily relate to clinical efficacy. This was a feature of the licensing of vaccines. The licence would have been granted on the basis of quality, safety and efficacy. The intended audience, general practioners, would not be misled by the claim.

The Panel considered that the claim was not unacceptable. No breach of Clauses 7.2, 7.3 and 7.8 of the Code was ruled.

Complaint received **6 October 1998**

Case completed **27 November 1998**

CASE AUTH/770/10/98 *NO BREACH OF THE CODE*

HOSPITAL PHARMACIST v LUNDBECK

Cipramil mailing

A hospital pharmacist alleged that a mailing on Cipramil (citalopram) sent by Lundbeck was unethical. The mailing asked readers to tick a box following the statement "I am now aware that, following its price reduction, Cipramil is the least expensive SSRI" and then sign the card. For every completed card a donation of £1 would be made to a charity.

The Panel had reservations about the mailing as, in effect, the payment to charity was for reading the mailing. The Panel decided that as the supplementary information to the Code permitted donations to charities in return for health professionals' attendance at company stands at meetings, it was difficult to draw a distinction for the mailing. The level of donation was not unreasonable. No breach of the Code was ruled.

A hospital pharmacist complained about a Cipramil (citalopram) mailing (ref 0998/CIP/511/067/RC) issued by Lundbeck Ltd. Included in the mailing was a card headed "Price reduction acknowledgement" which recipients were asked to complete and return to the company. Readers were required to tick a box which followed the statement "I am now aware that, following its price reduction, Cipramil is the least expensive SSRI" and then sign the card. In addition the card featured two cartoon characters with one character stating "Cipramil is now the least expensive SSRI". Readers were invited to add their reaction to the empty thought bubble of the second character. It was stated in the top left-hand corner that for every completed reply card returned to Lundbeck, the company would donate £1 to Depression Alliance.

COMPLAINT

The complainant considered it to be unethical for a pharmaceutical company to require pharmacists to read and acknowledge marketing material in order to ensure a donation to a charitable body (in this case Depression Alliance) from that company. The complainant stated that he had discussed this point with his colleagues who received the same literature and they were equally concerned.

RESPONSE

Lundbeck stated that the mailing was directed to all doctors and pharmacists involved in the prescribing and dispensing of antidepressant medication. It contained

important information detailing the recent price reduction of Cipramil of relevance to all the above. Whilst the company considered this a highly significant initiative in the treatment of depressive disorders, the aim of the reply card was to receive feedback from customers on the importance of this development. Lundbeck emphasised that the decision to respond was entirely voluntary and all replies would result in a charitable donation. Donations to charity made by companies in return for providing information were permissible provided that the level of donation was modest and the money was for a reputable charity. Lundbeck contended that £1 per reply and Depression Alliance fulfilled this criteria.

Lundbeck stated that it strongly disagreed that the mailing constituted an unethical activity and maintained that such methods of information gathering were legitimate and within the scope of the Code.

PANEL RULING

The Panel noted the supplementary information to Clause 18.1 "Donations to Charities" which stated that "Donations to charities made by companies in return for health professionals' attendance at company stands at meetings or offered as rewards for completing and returning quiz cards in mailings....are not unacceptable..... provided that the level of donation for each individual is modest, the money is for a reputable charity and any action required by the health professional is not inappropriate. ..... At all times the provisions of Clauses 2 and 9.1 must be kept in mind"

Clause 9.1 required that all materials and activities must recognise the special nature of medicines and the professional standing of the audience to which they were directed and must not be likely to cause offence. High standards must be maintained at all times. The supplementary information to Clause 9.1 stated that certain types, styles and methods of promotion, even where they might be acceptable for the promotion of products other than medicines, were unacceptable.

The Panel noted that the reply card in question asked the reader to acknowledge the fact that Cipramil was the least expensive SSRI. In the Panel's view the cartoon which was to be completed was more likely to elicit a flippant response than to provide the company with genuine feedback. In effect the payment to charity was for reading the mailing. The Panel had reservations about the mailing but decided that as the supplementary information to Clause 18.1 of the Code permitted donations to charities in return for health professionals' attendance at company stands at meetings it was difficult to draw a distinction between this and the mailing in question. The level of donation at £1 per card was not unreasonable. The Panel therefore ruled no breach of Clauses 9.1 and 18.1 of the Code.

Complaint received **7 October 1998**

Case completed **24 November 1998**

CASE AUTH/771/10/98 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER v PFIZER

Diflucan journal advertisement

A general practitioner complained about a journal advertisement for Diflucan (fluconazole) issued by Pfizer. The advertisement promoted the product for vaginal thrush and stated "Happiness is ....The Doctor who prescribed Diflucan 150 instead of a topical treatment she'd already tried" adjacent to a cartoon of a doctor and his patient. The complainant alleged that the advertisement suggested an indication for which Diflucan was not licensed. It was licensed only for use in vaginal candidiasis but it was reasonable to assume from the advertisement that it had a specific licence for failure of topical imidazole treatments. Failure of topical imidazole treatments was most likely to mean that there was some cause other than *Candida*.

The Panel considered that it was not clear whether the claim ".... instead of a topical treatment she'd already tried" referred to a previous episode of vaginal candidiasis or a current episode. The Panel did not consider however that the advertisement implied that Diflucan 150 had a specific licence for failure of topical treatment. In the Panel's view, the advertisement predominantly related to patient preference and convenience of oral treatment. The advertisement included a photograph of a capsule next to a mouth to show that Diflucan 150 was an oral treatment. The Panel ruled no breach of the Code.

A general practitioner complained about an advertisement for Diflucan (fluconazole) (ref 51841 March 1998) issued by Pfizer Limited which had appeared in GP, 2 October. The advertisement promoted the product for the treatment of vaginal thrush and featured a cartoon of a doctor and his female patient with the headline "Happiness is..... The Doctor who prescribed Diflucan 150 instead of a topical treatment she'd already tried".

COMPLAINT

The complainant alleged that the advertisement suggested an indication for which Diflucan was not licensed. As stated in the prescribing information, the product was licensed for use in vaginal candidiasis, however, it was reasonable to assume from the body of the advertisement that it had a specific licence for failure of topical imidazole treatments.

The complainant stated that in general practice imidazole resistance in *Candida* remained fairly low and because there had been reports of significant fluconazole

resistance, local advice was certainly to use itraconazole in these cases. However, it was far more likely in the clinical situation of failure of topical imidazoles that the reason for failure was that the vaginitis was due to some cause other than *Candida*. As the most likely cause was anaerobic vaginitis or *Trichomonas*, it would be perfectly reasonable to suggest that metronidazole was actually the treatment that the doctor in the cartoon should have been prescribing.

RESPONSE

Pfizer submitted that the objective of the advertisement was to show Diflucan 150 as a treatment for vaginal thrush in patients who might have already tried a topical over-the-counter (OTC) product. Dissatisfaction with topical treatments might not be due only to failure to eradicate the causative agent but also due to other factors, such as convenience of use. The patient, having already tried topical medication, might want to try a different method of administration of a suitable treatment. Pfizer did not consider that the advertisement implied in any way that the product had a specific licence for treatment after failure of topical medication. Rather, that it was a convenient alternative treatment for vaginal thrush, being a single oral dose which could be taken at any time.

Pfizer stated that the majority of British women suffered from vaginal candidiasis at some time and might have recurrent disease, where the most common causative agent was *Candida albicans*. On evidence to date, fluconazole-resistant *C.albicans* strains arising during the treatment of vaginal candidiasis with fluconazole were very rare indeed. There was no published literature indicating that single dose azole therapy for vaginal candidiasis was associated with the development of resistant *C.albicans* strains or resistant non-albicans *Candida* species. There was only one report of azole-resistant vaginal candidiasis caused by *C.albicans* in an immunocompetent patient (Sobel 1996). This was a patient with continuous vaginal candidiasis over 3 months and who had received both OTC topical agents as well as prescribed terconazole and fluconazole. The company therefore disagreed with the statement made in the complaint concerning "significant fluconazole resistance" in this patient population.

Pfizer did not disagree with the complainant's statement concerning the possibility that the patient's continuing symptoms might be due to a causative agent other than *Candida*, although anaerobic vaginitis and *Trichomonas* infection symptoms were not exactly the same as those of vaginal thrush. These conditions would be among the differential diagnosis for the doctor to consider in such a case. Consulting a doctor after any failure of self-medication could only be beneficial and the company considered that the advertisement endorsed this sensible approach.

PANEL RULING

The Panel noted the allegation that the advertisement promoted the use of Diflucan 150 when topical imidazole treatments had failed and this was not a licensed indication. The Panel noted Pfizer's submission that the intent of the advertisement was to show Diflucan 150 as a treatment for vaginal thrush in patients who might have already tried a topical OTC product and that dissatisfaction with topical treatments might not be due only to failure to eradicate the causative agent but also due to other factors such as convenience of use.

The Panel accepted that it was not clear whether the claim "... instead of a topical treatment she'd already tried" referred to a previous episode of vaginal candidiasis or referred to a current episode of vaginal candidiasis. The Panel did not consider however that the advertisement implied that Diflucan 150 had a specific licence for failure of topical treatment. In the Panel's view the advertisement predominantly related to patient preference and convenience of oral treatment. The advertisement included a photograph of a capsule next to a mouth to show that Diflucan 150 was an oral treatment. The Panel ruled no breach of Clauses 3.2 and 7.2 of the Code.

Complaint received **9 October 1998**

Case completed **24 December 1998**

CASES AUTH/772/10/98 & AUTH/773/10/98

DIRECTOR v EISAI AND PFIZER

Breach of undertaking

A general practitioner who had complained previously about the promotion of Aricept (donepezil) by Eisai and Pfizer alleged that the companies were continuing to use an advertisement which had been ruled in breach of the Code. The matter was taken up by the Director of the Authority as a complaint under the Code.

The Panel noted that the companies had taken action to comply with their undertakings given in June 1998 and the advertisement had been withdrawn. At that time the advertisement had already been placed for publication in the Royal College of General Practitioners Members' Reference Book 1998/9 which was not distributed until October 1998. The companies had overlooked the advertisement in June 1998 when they had withdrawn the others as it had been placed outwith their normal system for placing advertisements.

The Panel ruled each company in breach of the Code for failing to comply with its undertaking. The Panel noted that the advertisement had been placed directly with the publishers and it appeared that the companies did not have a system to identify and withdraw such one-off placements. The advertisement had been placed in a year book in April 1998 at a time when it was about to be the subject of an appeal and in the Panel's view extra care should have been taken to ensure that it could have been withdrawn if necessary.

The Panel considered that the failure to comply with the undertakings brought discredit upon and reduced confidence in the pharmaceutical industry in breach of Clause 2 of the Code. It also decided to report Eisai and Pfizer to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board noted that the companies had acted immediately to change their procedures. The companies had been open and honest in acknowledging the serious error and reassured the Appeal Board that such an error would not happen in the future. The Appeal Board noted that the companies had been ruled in breach of Clause 2 which was a sign of particular censure.

The Appeal Board considered that in the circumstances no further action was necessary.

COMPLAINT

The general practitioner who was the complainant in Cases AUTH/651/11/97 and AUTH/652/11/97 complained that Eisai Limited and Pfizer Limited were continuing to use an Aricept (donepezil) advertisement which included the claim "Mum has Alzheimer's... but she knew I was calling today." The Panel originally ruled no breach of the Code in cases AUTH/651/11/97 and AUTH/652/11/97 but in May 1998, on appeal by the complainant, the Appeal Board considered that the claim gave the impression that the patient's memory improved following treatment with Aricept. There was, however, insufficient data to support this impression and the Appeal Board ruled a breach of Clause 7.2.

The complainant stated that in October 1998 he had received a copy of the Royal College of General Practitioners (RCGP) Members' Reference Book 1998/99 in which the advertisement appeared. He had understood that the advertisement was no longer to be published after 10 June 1998 pursuant to the undertaking provided in Cases AUTH/651/11/97 and AUTH/652/11/97.

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

RESPONSE

Eisai responded on behalf of both companies. Eisai acknowledged that the advertisement was the one which was at issue in Cases AUTH/651/11/97 and AUTH/652/11/97 and subsequently ruled to be in breach of the Code. An undertaking had been given by Eisai, the market authorisation holder, stating that the advertisement would no longer be used. A similar undertaking had been given by Pfizer. A letter had also been provided listing the last publications in which the advertisement was to appear.

Eisai stated that the list of publications did not contain the RCGP Members' Reference Book, the publishers of which unfortunately were not contacted and requested to remove the advertisement. Eisai apologised for this oversight.

For advertising purposes, Eisai and Pfizer retained the services of two companies, an advertising agency and a purchaser of advertising space. Usually the purchaser would place advertisements supplied to it by the advertising agency. When the original advertisement was found to be in breach in June 1998, the advertising agency requested the purchaser to withdraw all the relevant advertisements. Unfortunately the advertisement in question was not placed via the usual route. It was requested directly by the publishers of the RCGP Members' Reference Book in April 1998 and the advertising agency provided a copy of the advertisement because it was still valid at that time. However there was a delay in the publication of the Reference Book for reasons of which the companies had no knowledge. The Reference Book was not subsequently published until September 1998, following the Appeal Board ruling. Therefore when the companies took action to withdraw all the relevant advertisements in June 1998, the purchaser was not in a position to withdraw the advertisement in question as it had no knowledge of its existence, a factor that Eisai and Pfizer acknowledged.

Eisai stated that in light of this regrettable incident, it and Pfizer had undertaken an audit with the advertising agency to ensure that no other *ad hoc* advertisements had been overlooked. This had been completed and the

companies could assure the Panel that there were no advertisements still in use which breached the Code. Further, a review of the standard operating procedures in place regarding the purchasing of advertising space would be instigated so that in future *ad hoc* requests such as the one from the publishers of the Reference Book would be administered through the same procedure as all other advertising.

Eisai stated that the inclusion of the advertisement was an unfortunate oversight and had only affected one publication. Further, it seemed clear that there was no intention to mislead or gain a commercial advantage by deliberately not removing the advertisement. Therefore the company submitted that no discredit had been brought upon nor had any confidence been reduced in the pharmaceutical industry as a result of the matter and therefore there was no breach of Clause 2 of the Code.

PANEL RULING

The Panel noted that the Aricept advertisements with the claim "Mum has Alzheimer's....but she knew I was calling today" had been considered by the Panel in Cases AUTH/561/5/97 and AUTH/562/5/97, AUTH/651/11/97 and AUTH/652/11/97 and AUTH/659/12/97 and AUTH/660/12/97.

Cases AUTH/561/5/97 and AUTH/562/5/97 arose from a letter in the British Medical Journal which had been critical of the promotion of Aricept and alleged that the advertisement suggested an unrealistic improvement in the mental status of patients. The Panel had ruled no breach of the Code and that ruling was not appealed to the Code of Practice Appeal Board.

In November 1997 the general practitioner who had pointed out that the Aricept advertisement was still being used had complained about the advertisement (Cases AUTH/651/11/97 and AUTH/652/11/97) alleging that there was no data to show that carers would notice an improvement in a patient's Alzheimer's disease because of treatment with the medicine. A month later another critical letter in the British Medical Journal made similar allegations which gave rise to two other cases, AUTH/659/12/97 and AUTH/660/12/97. The four cases were considered together and the Panel's ruling of no breach was appealed by both complainants. In May 1998 the Appeal Board ruled the advertisements to be in breach of Clause 7.2 of the Code.

The Panel noted that Eisai and Pfizer had taken action to comply with undertakings given in Cases AUTH/651/11/97 and AUTH/652/11/97 and Cases AUTH/659/12/97 and AUTH/660/12/97. Through their agents the companies had withdrawn relevant advertisements. The advertisement in question, however, had been placed via an unusual route for these companies and so was overlooked by them. Eisai and Pfizer had therefore failed to comply with their undertakings. The Panel ruled each company in breach of Clause 21 of the Code.

The Panel considered whether or not there had also been a breach of Clause 2 of the Code in view of the fact that the publication of the advertisement represented a failure to comply with an undertaking previously given. The Panel noted that the advertisement had been placed in April 1998. The companies had been notified of the complainant's intention to appeal in Cases AUTH/651/11/97 and AUTH/652/11/97 in February 1998. Due to a deferment the appeal was not heard until early May and the case was completed on 1 June 1998. The Panel noted that the advertisement had thus been submitted for publication in a year book which would be retained by the recipients, at a time when it was about to be the subject of an appeal. In the Panel's view extra care should have been taken to ensure that, if the appeal was successful and the advertisement was ruled to be in breach of the Code, the advertisement could have been withdrawn from an item with such high retention value. The Panel also noted that the advertisement had been placed via an unusual route and it appeared that the companies did not have a system to identify and withdraw such one-off placements. The Panel considered that overall the companies' actions brought discredit upon, and reduced confidence in, the pharmaceutical industry and therefore ruled a breach of Clause 2 of the Code.

The Panel noted that the Constitution and Procedure required it to report a company to the Appeal Board if it failed to comply with the procedures or if its conduct in relation to the Code warranted consideration by the Appeal Board (Paragraphs 8.1 and 8.2). The Panel considered that the circumstances warranted reporting Eisai and Pfizer to the Appeal Board.

COMMENTS FROM EISAI AND PFIZER

Both companies apologised sincerely for the failure to comply with the undertakings. Action had been taken to change procedures within the companies to ensure that the problem would not happen again.

The companies used the services of a media buyer and on rare occasions as in this instance the companies were asked directly for an advertisement. This had been supplied and had regrettably been overlooked when withdrawing the advertisement following the Appeal Board's ruling of a breach of the Code. The companies acknowledged that there would have been sufficient time to withdraw the advertisement from the RCGP Members' Reference Book. The publication of the advertisement was due to human error. The companies pointed out that in June 1998 when the undertaking had been given it had, at short notice, managed to replace the advertisement in question with a corporate advertisement in some of the publications scheduled to carry the Aricept advertisement.

It was explained that in future all advertisements would be placed via a single media buyer. There would be no *ad hoc* placing of advertisements. Both companies were fully committed to the Code and fully appreciated the importance of undertakings.

APPEAL BOARD CONSIDERATION

The Appeal Board considered that an undertaking was an important document. It required companies to provide details of the action taken and the date of final use of materials ruled in breach. It was signed by the chief executive or with their authority and included a statement that all possible steps would be taken to avoid similar

breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Appeal Board noted that the companies had already changed their procedures to ensure that problems would not be repeated. The Appeal Board was extremely concerned that the advertisement had been used again. The Panel had ruled a breach of Clause 2 which was a sign of particular censure.

The Appeal Board noted that Eisai and Pfizer had acted immediately to change their procedures. The companies had been open and honest in acknowledging the serious error and had reassured the Appeal Board that they were fully committed to the Code and that such errors would not happen in the future.

The Appeal Board decided that in the circumstances no further action was necessary.

Proceedings commenced	**14 October 1998**
Undertakings received	**8 and 9 December 1998**
Appeal Board consideration	**16 December 1998**

CASE AUTH/774/10/98

SMITHKLINE BEECHAM v BAYER

Ciproxin "Dear Doctor" letter

SmithKline Beecham complained about a Ciproxin (ciprofloxacin) "Dear Doctor" letter issued by Bayer. The letter was headed "Working in comparison with co-amoxiclav" and concerned the treatment of lower respiratory tract infections (LRTIs). SmithKline Beecham marketed Augmentin (co-amoxiclav).

The table headed "% *H.influenzae* blood culture isolates (sensitive)" gave data for Ciproxin and co-amoxiclav for 1989, 1991 and 1994. SmithKline Beecham questioned the significance of using blood culture isolates of *H. influenza* in assessing the relative benefits of ciprofloxacin and co-amoxiclav in eradicating this pathogen in community LRTIs. The data was used to claim an increase in *H. influenza* resistance to co-amoxiclav. It could not be assumed that blood culture isolates bore any similarity to isolates from sputum. SmithKline Beecham alleged that it was inappropriate and misleading to use this data in the context of community LRTIs as seen by general practitioners. The Panel noted a previous case (AUTH/479/12/96) which concerned an allegation that it was misleading and irrelevant to use *H. influenzae* blood isolate resistance data in support of respiratory tract infection in the community. The Panel had considered that it would be clear to readers that blood culture isolates had been used for the sensitivity tests. No breach of the Code had been ruled. Considering the present case, the Panel noted that both the text of the "Dear Doctor" letter and the table clearly stated that the sensitivity tests were derived from blood culture isolates. The Panel ruled no breach of the Code.

The letter stated "In practice, Ciproxin yielded a superior bacterial eradication rate in lower respiratory tract infections compared to co-amoxiclav (100% vs 87.5%, p<0.01), whilst recording at least equal clinical success rates", a claim which was referenced to a paper by Barash *et al* which included a similar statement. SmithKline Beecham alleged that the clinical data in the paper did not support either statement. The Panel noted that the study in question was conducted to compare the clinical and bacteriological efficacy and safety of oral ciprofloxicin with co-amoxiclav in the treatment of lower respiratory tract infections in adults. The paper stated that favourable clinical response rates (defined as resolution plus improvement) were comparable between ciprofloxacin (94%) and co-amoxiclav (95%) treated patients. The Panel noted that 66% of the ciprofloxacin group achieved complete resolution compared with 78% of the co-amoxiclav group. The Panel noted that whilst the bacterial eradication rates were statistically significant in favour of ciprofloxacin, clinical resolution rates, whilst not statistically significant, were numerically in favour of co-amoxiclav. The Panel noted that the claim "at least equal clinical success rates" was referenced to the paper but considered that it implied that ciprofloxacin resulted in equal or higher clinical success rates than co-amoxiclav. The Panel considered that the claim was misleading and ruled a breach of the Code.

SmithKline Beecham Pharmaceuticals complained about a Ciproxin (ciprofloxacin) "Dear Doctor" letter (ref GP7) issued by Bayer plc Pharmaceutical Division. The letter was headed "Working in comparison with co-amoxiclav" and gave information regarding the treatment of lower respiratory tract infections (LRTIs). SmithKline Beecham marketed Augmentin (co-amoxiclav).

1 Use of data relating to the sensitivity of *H. influenzae* blood culture isolates.

The letter featured a table headed "% *H. influenzae* blood culture isolates (sensitive)" which gave data for Ciproxin and co-amoxiclav for 1989, 1991 and 1994. The percentage of isolates sensitive to Ciproxin in those years was 100, 99.5 and 100 respectively. The corresponding figures for co-amoxiclav were 98.9, 98.2 and 94.8.

COMPLAINT

SmithKline Beecham questioned the significance of using blood culture isolates of *H. influenzae* in assessing the relative benefits of ciprofloxacin and co-amoxiclav in eradicating this pathogen in community LRTIs. This data

was used to claim an increase in *H. influenzae* resistance to co-amoxiclav. SmithKline Beecham stated that it could not be assumed that blood culture isolates bore any similarity to *H. influenzae* isolates from sputum.

SmithKline Beecham alleged that it was inappropriate and misleading to use this data in the context of community LRTIs seen by general practitioners, which was the subject of the mailing. This point was also made in the data on file provided by Bayer in which a professor of clinical bacteriology stated that "the *Haemophilus influenzae* figures refer to blood culture isolates, and I think that this should be mentioned in your document, because these are not really typical of most *H. influenzae* strains causing chest infection"

SmithKline Beecham stated that, in intercompany correspondence, Bayer had referred to a previous complaint made by SmithKline Beecham (Case AUTH/479/12/96) where this data was ruled not to be in breach of Clause 7.2 of the Code. SmithKline Beecham maintained that whilst the use of blood culture data might be clinically relevant in seriously ill patients, the use of this blood culture data in the context of community LRTIs, in general, was not appropriate and therefore misleading. Indeed, more recently published data, Felmingham *et al* (1998), suggested that resistance had not developed amongst community-acquired *H. influenzae* isolates from the lower respiratory tract. Of 1078 isolates collected from geographically disparate regions in the UK 98.8% were found to be sensitive to co-amoxiclav

RESPONSE

Bayer referred to the similar complaint made by SmithKline Beecham, Case AUTH/479/12/96, in which Bayer was ruled not to be in breach of Clause 7.2. Bayer considered that it had made it perfectly clear in the table of the "Dear Doctor" letter, as on the original advertorial, that the *H. influenzae* data referred to blood culture isolates, and not sputum. The company did not consider that the letter implied or suggested that blood isolates were identical to sputum isolates, but left it to the doctor to draw his own conclusions. Bayer noted that SmithKline Beecham claimed that resistance had not developed amongst community acquired *H. influenzae* isolates but Shanahan *et al* (1996) and Doern *et al* (1997) had shown that resistance was developing to co-amoxiclav regardless of the source of *H. Influenzae* isolate.

PANEL RULING

The Panel noted that Case AUTH/479/12/96 concerned an allegation that it was misleading and irrelevant to use *H. influenzae* blood isolate resistance data in support of respiratory tract infection in the community. The advertisement had specified the population with the bacteraemia studied. The Panel had considered that it would be clear to readers that blood culture isolates had been used for the sensitivity tests. No breach of the Code had been ruled. The Panel considered that this case was similar to the previous case.

Considering the present case the Panel noted that both the text of the "Dear Doctor" letter and the table clearly stated that the sensitivity tests were derived from blood culture isolates. The Panel ruled no breach of Clause 7.2 of the Code.

2 Claim "Ciproxin yielded a superior bacterial eradication rate in lower respiratory tract infection compared to co-amoxiclav....at least equal clinical success rates"

The "Dear Doctor" letter stated that "In practice, Ciproxin yielded a superior bacterial eradication rate in lower respiratory tract infection compared to co-amoxiclav (100% vs 87.5%, $p<0.01$), whilst recording at least equal clinical success rates". The claim was referenced to a paper by Barash *et al* (1991).

COMPLAINT

SmithKline Beecham questioned Bayer's use of the paper by Barash *et al* (1991) to reference the claim "at least equal clinical success rates" for ciprofloxacin and co-amoxiclav in LRTIs. In intercompany correspondence, Bayer had noted that a similar statement was made in the Barash paper which stated that "the clinical efficacy of ciprofloxacin was at least equal to that of amoxicillin/clavulanate [co-amoxiclav]".

SmithKline Beecham stated that the clinical data presented in the Barash paper did not support either statement. The study reported that there was not a statistically significant difference in resolution plus improvement, with 94% reported for ciprofloxacin and 96% for co-amoxiclav. In fact, there was a trend towards greater resolution with co-amoxiclav (78%) than ciprofloxacin (66%). Using the words "at least" when referring to this study implied that ciprofloxacin might be more clinically effective than co-amoxiclav in treating LRTIs. SmithKline Beecham alleged that this was misleading.

SmithKline Beecham noted that, again in intercompany correspondence, Bayer had referred to the previous complaint (Case AUTH/479/12/96) where a similar claim was ruled not to be in breach. SmithKline Beecham noted in that instance, however, that the wording of the claim was "....showing similar clinical results". This had a very different meaning to "at least equal clinical success rates". A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Again Bayer referred to the similar complaint made by SmithKline Beecham, Case AUTH/429/12/96, in which no breach of Clause 7.2 was ruled

Bayer stated that the efficacy of antibiotic medicines had been defined in three ways by Davis *et al* (1996); *clinical cure:* resolution of signs and symptoms of infection without recurrence; *clinical improvement:* signs and symptoms show improvement from baseline; *bacterial eradication:* complete eradication of the pathogen without recurrence, reinfection or super infection.

The company stated that it was totally appropriate to use bacteriological eradication rates to highlight different outcomes between antibiotic therapies.

Bayer agreed that the wording was slightly different on this occasion. However, the company stated that this was exactly what was written in the paper.

PANEL RULING

The Panel noted that Barash *et al* (1991) was a study conducted to compare the clinical and bacteriological efficacy and safety of oral ciprofloxacin with amoxicillin/clavulanate in the treatment of lower respiratory tract infections in adults. Barash *et al* stated that favourable clinical response rates (defined as resolution plus improvement) were comparable between ciprofloxacin (94%) and amoxicillin/clavulanate (96%) treated patients. The Panel noted that 66% of the ciprofloxacin group achieved complete resolution compared with 78% of the amoxicillin/clavulanate group. The Panel noted that whilst the bacterial eradication rates were statistically significant in favour of ciprofloxacin, clinical resolution rates, whilst not statistically significant, were numerically in favour of amoxicillin/clavulanate.

The Panel noted that the claim "at least equal clinical success rates" was referenced to the Barash *et al* study but considered that it implied that ciprofloxacin resulted in equal or higher clinical success rates than co-amoxiclav. Given the data the Panel considered that the claim was misleading and ruled a breach of Clause 7.2 of the Code.

Complaint received **15 October 1998**

Case completed **21 December 1998**

CASE AUTH/775/10/98 *NO BREACH OF THE CODE*

CONSULTANT PAEDIATRICIAN/ENDOCRINOLOGIST v FERRING

Information requested by patient's mother

A consultant paediatrician/endocrinologist complained about the activities of Ferring in relation to its product Medi-Jector, a no needle device for administering its growth hormone Zomacton (somatropin). He had received a letter from a home support company referring to a named patient whose mother had requested that information about the device be sent to him. She had seen it at a Child Growth Foundation Day and considered that her son might prefer it. The letter said that its author would be grateful if the complainant would consider showing the device to the family concerned and assistance could be given with this by one of the home support company's nurses. A Ferring representative would contact the complainant shortly to show the device to him and his department. The complainant said that he already had experience of using the device. He accepted that patients might seek information, but considered that this should be on the basis of "maybe you would like to discuss this with your supervising clinician" and not "this would be a much better system and we will get in touch with your clinician for you".

The home support company was an independent company contracted by Ferring to provide a home support service for Zomacton. Ferring was responsible under the Code for the company's activities in this regard. Ferring had not been represented at the Child Growth Foundation Day, but, following that, it had been contacted by the patient's mother about obtaining the device and the enquiry had been passed on to the home support company. The Panel noted that, at the Child Growth Foundation Day, all available devices had been demonstrated by hospital nurses.

The Panel noted that the Code suggested that requests from patients for information might, in some instances, best be handled by passing the information to the patients' doctors for discussion, rather than direct to the patients. The patient's mother had been advised by the home support company to discuss the matter with the complainant and, in the Panel's view, that was an appropriate course of action. In the Panel's view, it would have been preferable if the letter to the complainant had simply provided the information and left it for the complainant to contact the company if further information, or a visit, were required.

The Panel considered that overall it appeared that the patient's mother had not been directed towards a specific product. The Panel noted Ferring's submission that during the conversation between the patient's mother and the home support company, it became apparent that the Medi-Jector might well not be an appropriate choice for the patient. There was no evidence that Ferring itself or the home support company had advertised the product to the general public and nor had they encouraged the patient's mother to ask for it to be prescribed. The Panel ruled that there had been no breach of the Code.

A consultant paediatrician/endocrinologist complained about the activities of Ferring Pharmaceuticals Ltd in relation to its Medi-Jector, a no needle injection device for administering its growth hormone Zomacton (somatropin). The letter was written to a home support company and had been copied to the Authority.

COMPLAINT

The complainant stated that he was surprised to receive a letter from the home support company concerning one of his patients who attended his paediatric endocrine clinic. The patient was on treatment with growth hormones.

The letter in question was from the disease management co-ordinator at the home support company. The letter stated that information on the growth hormone, Zomacton, and the service that was included in the NHS cost of the medicine, was enclosed. The letter referred to

the patient by name who had requested that the information be sent to the complainant because of the device that was used with this particular growth hormone. The letter stated that the Medi-Jector was the only no needle system on the market and the patient's mother considered that her son might prefer the device. The patient's mother had seen the Medi-Jector at a Child Growth Foundation Day recently and had consequently got in touch with Ferring which contacted the home support company as it operated the home care service on behalf of Ferring. The letter stated that the author would be grateful if the complainant would consider showing the device to the family concerned and that one of the nurses at the home support company would be happy to spend some time with the patient letting him have a proper look at the device. The letter concluded that a representative from Ferring would be contacting the complainant shortly to show it to him and his department.

The complainant stated that he was particularly surprised as he was in regular and close contact with the Ferring representative, the department had previous experience of using the Medi-Jector device for administering the growth hormone and already made decisions in terms of growth hormone treatment and injection device based on what was best for an individual patient and what that patient and family chose from the devices available. The complainant considered it was unnecessary for the representative from Ferring to contact him to show him and his department the device. They were already familiar with it and this would comprise an unsolicited approach to change treatment to a specific product in a specific patient. The complainant considered this was probably against the Code.

The complainant accepted that wide dissemination of patient information was of course extremely important and that if the company had a stand at one of the Growth Foundation meetings it was of course very likely that patients would approach it for further information. The complainant did not accept that the patient or family should be directed towards a specific product which was implied in the second paragraph of the letter. Certainly information should be given but treatment decisions were often made on a multi-factorial basis. The advice should be "maybe you would like to discuss this with your supervising clinician" and not "this would be a much better system and we will get in contact with your clinician for you".

The complainant stated that patient confidentiality prevented him from going into details, but the decision to treat the particular patient with a needle injection system was made on the basis of past history, clinical condition and other surrounding circumstances, which made the Medi-Jector system unsuitable for this particular patient. The complainant stated that he would be happy to discuss the situation with the patient's mother when she next attended a clinic and, as and when conditions changed, to make the Medi-Jector device suitable, the complainant would be happy to organise a change of prescription if that was what the family wanted.

The complainant had copied his letter to Ferring as he was concerned that this specific approach to marketing was unethical and counter productive to good clinician/pharmaceutical company relationships.

RESPONSE

Ferring stated that it had already investigated the events which led to the letter from the complainant to the home support company.

The mother of the patient who was receiving treatment with growth hormone attended a Child Growth Foundation Day which was held on Saturday, 29 August. Ferring had declined an invitation to attend this meeting.

The company enclosed a copy of the programme for the Child Growth Foundation Day which included a presentation of administration devices given by two specialist growth nurses. The purpose of the presentation was to demonstrate to patients and their parents the use of a range of currently available injection devices, one of which was the Medi-Jector. In fact demonstrations of this nature had been a feature of meetings held by the Child Growth Foundation for many years and they provided a valuable source of independent information for patient groups.

Ferring provided no assistance whatsoever for the presentation. It did not provide Zomacton or a Medi-Jector for the demonstration and nor did it provide any literature for distribution to patients at the meeting.

On 4 September the patient's mother contacted Ferring requesting information on how she could obtain a Medi-Jector for her son who was currently receiving treatment with injected growth hormone. When approached in this way by a member of the general public a representative of a pharmaceutical company might provide non-promotional information so long as it was factual, balanced, objective and did not induce a patient to request their doctor to prescribe a specific product. The patient's mother was referred to an independent home healthcare company contracted by Ferring solely to provide a comprehensive service of home support for prescribed users of Zomacton. The home support company provided specialised technical support for patients who had been prescribed Zomacton and were not involved in any marketing activities on behalf of Ferring. Skilled staff at the home support company were trained in the use of all appropriate delivery devices for growth hormone including the Medi-Jector and it was considered appropriate that they dealt with this particular enquiry.

In a telephone conversation with the disease management co-ordinator from the home support company, the patient's mother explained that she had seen a demonstration of the Medi-Jector and wanted to know how to obtain the device for her son. She did not require any information on the device because she had no further questions to raise following the demonstration at the Child Growth Foundation Day. The patient's mother thought it would be possible to simply transfer her son to the Medi-Jector in place of the needle based device he was currently using. It was explained that this was not possible and that the doctor was the only person who could make that decision. She was advised to discuss choice of delivery device with her doctor, the complainant. In fact, during the course of the conversation, the patient's mother briefly described some of her son's circumstances and it became apparent that

the Medi-Jector might well not be an appropriate choice. There was no effort made on the part of the disease management co-ordinator from the home support company to advise the patient's mother that any one treatment or device was a better choice, only that she should discuss the matter with her son's doctor at their next visit. In order to facilitate the process it was agreed that the disease management co-ordinator would provide the current relevant information to the complainant.

Following this conversation, on 9 September the disease management co-ordinator sent the letter to the complainant in which she explained that the patient's mother had seen the Medi-Jector and considered that her son might prefer the device to his current administration system. The letter was accompanied by information on Zomacton together with details of the home healthcare service to provide the complainant with the information necessary to evaluate the request. Ferring accepted that the letter might be subject to misinterpretation but believed that in the light of the details surrounding the case it was clear that there was no breach of the Code and that all staff had acted responsibly.

The head of technical affairs at Ferring had discussed the matter with the complainant who had accepted this explanation of events and was satisfied that the patient's mother was not directed to ask for the Medi-Jector or Zomacton by Ferring or the home support company. A copy of the letter sent to the complainant was provided. This letter discussed the complainant's concerns and stated that the patient's mother should discuss any change to her son's treatment with his doctor.

Ferring had no formal relationship with the Child Growth Foundation. It had, in common with other manufacturers/distributors of growth hormone, occasionally supported educational and training meetings run by the Child Growth Foundation. These meetings were general in nature and not linked to any one product. During 1998 Ferring had made a donation to the Child Growth Foundation to support a national consensus meeting on measuring guidelines, payment for pictures showing the correct method for measuring growth in children, and support for a training day on measuring and screening for health visitors and community nurses. The two specialist nurses who gave the demonstration of all available injection devices were from a children's hospital. Funding for one of the nurses was indirectly from Ferring through research grants made to the hospital in support of clinical trials. Ferring believed that the other nurse was funded by another growth hormone supplier.

The nurses had been invited by the Child Growth Foundation to demonstrate all available devices and similar meetings and demonstrations had been undertaken for many years.

Copies of a resource pack "Shaping the Future" sent to the complainant were provided. The resource pack included materials for both the doctor and the parent in relation to the home support company service as well as material about the product.

PANEL RULING

The Panel noted the supplementary information to Clause 20.3 of the Code relating to requests from the general public for information or advice on personal medical matters which stated that all such requests should be handled with great care and advised that requests from patients might in some instances best be handled by passing the information to the patients' doctors for discussion rather than direct to the patients concerned.

The Panel noted that the patient's mother had telephoned Ferring for information about obtaining the Medi-Jector. The request had been referred to the home support company. Ferring was responsible under the Code for the activities of the home support company. The Panel noted that the patient's mother had been advised by the home support company to discuss the matter with the complainant. In the Panel's view this was an appropriate course of action.

The Panel considered that the material sent by the home support company to the complainant was promotional. It did not accept Ferring's submission that the home support company was not involved in promoting the product as this was exactly what the mailing would do. The materials in the resource pack for the doctor promoted the product and prescribing information was included. In relation to the letter sent by the home support company, the Panel noted that Clause 1.2 of the Code exempted from the definition of promotion replies made in response to specific communications but only if they related solely to the subject matter of the enquiry, were accurate and did not mislead and were not promotional in nature. The letter had been sent in response to an enquiry from the patient's mother but the Panel considered that it could not take the benefit of the exemption as it was promotional in nature. The letter should have complied with all aspects of the Code including the need for it to bear prescribing information.

The Panel noted that it was acceptable under the Code for companies to write to doctors in relation to requests from members of the public. The Panel had some reservations about the letter in question. As noted above it was promotional and should have included the prescribing information. It was not necessarily a breach of the Code to send promotional material to the doctor in such circumstances. The Panel noted that the letter stated that "A Representative from Ferring Pharmaceuticals will be contacting you to show it to you and your department". In the Panel's view it might have been preferable if the letter had simply provided the information and left it for the doctor to contact the company if further information or a visit from a representative was required. In these particular circumstances this did not however constitute a breach of the Code.

The Panel noted that Ferring had given support to the Child Growth Foundation in the form of sponsorship for various activities. This was not necessarily unacceptable. Clause 18.1 of the Code and its supplementary information were relevant. One of the nurses who had demonstrated the devices had been funded by a research grant to the hospital from Ferring. The company had submitted that the nurses had demonstrated all available devices at the meeting. The Panel considered that patients and parents would be interested in a no needle device for administering growth hormone.

The Panel considered that overall it appeared that the patient's mother had not been directed towards a specific product. The Panel noted the submission from Ferring that during the conversation between the patient's mother and the home support company it became apparent that

the Medi-Jector might well not be an appropriate choice for the patient.

The Panel considered that this was a difficult case. Pharmaceutical companies were increasingly being asked for further information about their products. Such requests had to be dealt with in accordance with the Code which prohibited advertising of prescription only medicines and certain pharmacy medicines to the public. Companies could provide factual, balanced information to the public which complied with Clause 20.2 of the Code. Companies could not make statements for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine.

The Panel considered that overall there was no evidence that Ferring itself or via the home support company had advertised its medicine to the general public, nor had it encouraged the patient's mother to ask for the product to be prescribed. The Panel considered that, although the letter to the complainant was on the limits of acceptability, it did not amount to a breach of the Code as alleged. The Panel therefore ruled no breach of Clauses 20.1, 20.2 and 9.1 of the Code.

The Panel requested that its concerns regarding the lack of prescribing information on the letter be drawn to Ferring's attention. The Panel also queried whether the letter had been certified in accordance with Clause 14 of the Code.

Complaint received 20 October 1998

Case completed 5 January 1999

CASES AUTH/776/10/98 and AUTH/777/10/98

CONSULTANT PHYSICIAN v BRISTOL-MYERS SQUIBB and SANKYO PHARMA

Lipostat "Dear Doctor" letter

A consultant physician complained about a "Dear Doctor" letter concerning Lipostat (pravastatin) issued by Bristol-Myers Squibb and Sankyo Pharma. The letter, headed "Lipostat-low potential for drug interactions", stated that the recent withdrawal of mibefradil highlighted the importance of cytochrome P-450 in interactions and that unlike statins metabolised by cytochrome P-450 3A4, Lipostat metabolism was independent of cytochrome P-450. Cytochrome P-450 was involved in the metabolism of a number of commonly prescribed medicines and some of these were presented in a boxed list. Various statins were referred to in the letter but a footnote said that these might not interact with each of the medicines listed. The data sheets should be consulted. The complainant said that the letter was damaging the reputations of other statins where significant interactions had been exceedingly rare. The complainant considered that it was unhelpful, misleading and potentially harmful to patients to have this type of shroud waving to doctors.

Having reviewed the summaries of product characteristics (SPCs) for Lipostat and for the other statins mentioned, atorvastatin, cerivastatin, fluvastatin and simvastatin, the Panel considered that the letter was only partly correct with regard to potential interactions due to cytochrome P-450 interactions. The impression from the letter about potential interactions was misleading in the light of the detailed information in the SPCs. No mention was made of the clinical significance of any of the interactions. Some were just theoretical possibilities. Readers would not be able to judge the significance of the interactions from the letter. The Panel ruled that the letter was misleading with respect to potential interactions and disparaging of the other statins.

A consultant physician complained about the advertising of Lipostat (pravastatin) by Bristol-Myers Squibb Pharmaceuticals Limited and Sankyo Pharma UK Limited.

The material at issue was a "Dear Doctor" letter headed "Lipostat - low potential for drug interactions". The letter stated that the recent withdrawal of mibefradil highlighted the importance of cytochrome P-450 in drug-drug interactions as some of those reported were P-450 mediated. The letter stated that amongst the medicines implicated were the statins metabolised by cytochrome P-450 3A4 and that unlike other statins Lipostat (pravastatin) metabolism was independent of cytochrome P-450. Other statins were metabolised by cytochrome P-450 and, therefore, potentially might interact with a number of commonly prescribed medicines and even grapefruit juice. The letter included a boxed list headed "Cytochrome P-450 mediated drug interaction potential". The medicines listed were mibefradil, diltiazem, nifedipine, losartan, clarithromycin, cimetidine, fluoxetine and paracetamol. It was stated that the list was not comprehensive and the list was qualified by the use of an asterisk which explained that simvastatin, fluvastatin, atorvastatin and cerivastatin might not interact with each of the medicines listed. Readers were advised to check the data sheet.

COMPLAINT

The complainant pointed out that the problems with mibefradil highlighted the need to be aware of drug interactions, particularly prior to marketing.

The issue with the "Dear Doctor" letter, however, was that it implied that there were important cytochrome P-450 dependent problems with the use of atorvastatin, cerivastatin, fluvastatin and simvastatin, and that pravastatin was exempt from this. This effectively was damaging the reputation of other agents where significant interactions had been exceedingly rare. In practice, the number of important interactions when a statin was used was small, with the exception of the now withdrawn mibefradil.

There was a "get out" in the letter which stated that some of the statins might not interact with each of the medicines listed and to check the data sheet.

However, if one took fluvastatin for example, this was not primarily metabolised by CYP 3A4 enzyme as implied in the advertisement. Fluvastatin was metabolised primarily by the cytochrome P-450 2C9 isozyme. Fluvastatin had not been reported to give any clinically significant interactions with diltiazem, nifedipine, losartan, clarithromycin, cimetidine, fluoxetine, or paracetamol, as listed in the letter.

In respect of cerivastatin, there was no evidence from interaction studies that cerivastatin interfered with, or was interfered with by, the metabolism of other medicines which acted at cytochrome P-450 3A4.

Returning to the other statins mentioned, while there might be theoretical potential for the drug interactions mediated by the CYP 3A4 isozymes, very few were stated as being of clinical relevance in product literature.

It was unhelpful, misleading and potentially harmful to patients to have this type of shroud waving to doctors.

RESPONSE

Bristol-Myers Squibb and Sankyo submitted a joint response. Each of the complainant's concerns were dealt with in turn.

The complainant stated that the letter implied that there were important cytochrome P-450 dependent problems with the use of atorvastatin, cerivastatin, fluvastatin and simvastatin and that pravastatin was exempt from this, and that this was damaging the reputation of other agents.

Bristol-Myers Squibb and Sankyo submitted that it was clear from the summaries of product characteristics (SPCs) for atorvastatin, cerivastatin, fluvastatin and simvastatin that each of these products was metabolised by cytochrome P-450 and each of the SPCs stated the possibility of interaction with medicines that inhibited or were metabolised by the same isoenzyme. Pravastatin was the only statin which was not significantly metabolised by cytochrome P-450 and which had no potential for cytochrome P-450 mediated interaction with any of the medicines known to be metabolised by this system. Therefore pravastatin had a lower potential for side effects caused by these interactions than atorvastatin, cerivastatin, fluvastatin and simvastatin. The letter was written to highlight this difference between the various agents. The letter was written to make it very clear that the companies were talking about potential interactions with members of the statin class. The phrase used was ".... potentially may interact...". The content of the letter was entirely consistent with the SPCs for the statins and therefore did not disparage or mislead.

The complainant stated that fluvastatin was not primarily metabolised by cytochrome P-450 3A4 as implied in the advertisement and that fluvastatin had not been reported to give any clinically significant interactions with the medicines listed.

Bristol-Myers Squibb and Sankyo agreed with the complainant that fluvastatin was not metabolised by cytochrome P-450 3A4. However, the letter did not imply the contrary. All of the comparisons made between pravastatin and the other statins related to metabolism by the cytochrome P-450 family of enzymes, rather than specifically to the 3A4 isoenzyme.

It was clearly stated in a prominent position in the letter that fluvastatin might not interact with each of the medicines listed. Each of the medicines listed might interact with one or more of the statins listed. An exhaustive list would be too long and, for clarity, medicines that general practitioners would be familiar with were chosen for inclusion in the list. In the case of fluvastatin, the potential arose for interaction with losartan, which was a substrate of cytochrome P-450 2C9. When it was borne in mind that the SPC for fluvastatin warned of the theoretical possibility of medicine interactions with medicines metabolised by this isoenzyme, the companies submitted that this aspect of the letter was clear, balanced and not misleading.

The complainant asserted that there was no evidence from interaction studies that cerivastatin interfered with, or was interfered with by, the metabolism of other medicines which acted at cytochrome P-450 3A4.

Bristol-Myers Squibb and Sankyo pointed out that the cerivastatin SPC stated that caution should be exercised when co-prescribing cerivastatin with cytochrome P-450 3A4 inhibitors, citing erythromycin, itraconazole and cyclosporin as examples, although interaction studies had not been performed. The SPC also stated that the possible interaction with other substrates of this isoenzyme was unknown but should be considered for other medicines with a narrow therapeutic index. There was therefore the potential for interaction between cerivastatin and those medicines in the list that were metabolised by cytochrome P-450 3A4, which was the point made in the letter. The letter accurately reflected the SPC for cerivastatin and was therefore balanced, fair and objective and not disparaging to cerivastatin.

The complainant stated that for the other statins mentioned, while there might be theoretical potential for interactions mediated by the cytochrome P-450 3A4 isoenzymes, very few were stated as being of clinical relevance in product literature. The complainant suggested that the letter was unhelpful and misleading.

Bristol-Myers Squibb and Sankyo acknowledged that although it was true that interactions with the statins metabolised by cytochrome P-450 were rare, the risk posed by such interactions was clinically important. The recent withdrawal of mibefradil served as a timely reminder of the importance of drug-drug interactions mediated at the cytochrome P-450 3A4 isozyme. The "Dear Doctor" letter sent out by the manufacturer of mibefradil on its use with statins had specifically described cases of a rhabdomyolysis thought to be due to the increased bioavailability of simvastatin in patients co-prescribed mibefradil and simvastatin. In fact, several

patients had died due to this interaction. Following this the Food and Drugs Administration in the United States of America advised that, pending further information, use of mibefradil with atorvastatin or cerivastatin was "strongly discouraged".

More recently, concerns regarding drug-drug interactions in HIV patients taking protease inhibitors which were powerful inhibitors of cytochrome P-450, had been highlighted in The Lancet. A further example of a drug-drug interaction thought to be mediated via the cytochrome P-450 3A4 isoenzyme was a case of myositis and rhabdomyolysis in a patient taking simvastatin and nefazodone which interfered with the cytochrome P-450 3A system. Physicians were now much more aware of these interactions and the clinical importance of medicines metabolised by the cytochrome P-450 system. It was therefore reasonable to bring this potentially clinically important matter to the attention of UK physicians. Consequently, the letter was not unhelpful or misleading, and could not be described as "shroud waving".

In summary, the complainant acknowledged the need to be aware of interactions and Bristol-Myers Squibb and Sankyo agreed with this. At the time the letter was sent, there was a very real concern regarding the possibility for interaction between mibefradil and statins metabolised by cytochrome P-450 3A4, a concern highlighted in The Lancet. The letter was therefore used to bring to the attention of prescribing physicians an issue, potential interactions with statins, that was at the time clinically relevant and important. The companies were no longer using this letter.

PANEL RULING

The Panel noted that the letter referred to the importance of cytochrome P-450 in drug-drug interactions. Reference was made to statins metabolised by cytochrome P-450 3A4. According to the letter Lipostat metabolism was independent of cytochrome P-450. Other statins were metabolised by cytochrome P-450 including atorvastatin, cerivastatin, fluvastatin and simvastatin.

The Panel examined the Lipostat SPC which stated that no clinically significant effects were seen in a range of interaction studies. There was no mention of cytochrome P-450 in the SPC.

The Panel noted that the SPC for Lescol (fluvastatin) referred to *in vitro* findings showing a potential effect of fluvastatin on the activity of the P-450 CYP2C subfamily indicating the theoretical possibility of an interaction with medicines also metabolised by this subfamily, such as warfarin, sulphonylureas, diclofenac and phenytoin, if administered with fluvastatin, although the clinical significance was unknown. The SPC noted that an *in vivo* study with warfarin showed that fluvastatin had no effect on prothrombin times or warfarin blood levels.

The SPC for Zocor (simvastatin) stated that it was metabolised by the cytochrome P-450 isoform 3A4. Certain medicines had a significant inhibitory effect at therapeutic doses on this metabolic pathway. These included cyclosporin, the tetralol-class calcium channel blocker mibefradil, itraconazole, ketoconazole and other antifungal azoles, erythromycin, clarithromycin and nefazodone. The SPC also stated that the concommitant use with other medicines labelled as having a potent inhibitory effect on cytochrome P-450 3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweighed the increased risk. Phenazone was a model for medicines metabolised by the cytochrome P-450 system. Zocor had little or no detectable effect on the pharmacokinetics of phenazone in hypercholesterolaemic patients.

The SPC for Lipobay (cerivastatin) stated that the involvement of cytochrome P-450 CYP 3A4, besides others, in the metabolism of cerivastatin could be demonstrated by *in vitro* experiments. The co-administration of cimetidine (a non-specific cytochrome P-450 inhibitor) did not lead to any significant changes in cerivastatin pharmacokinetics. Interaction studies with P-450 3A4 inhibitors (erythromycin, itraconazole, cyclosporin) had not been performed and therefore caution was advised when co-prescribing these products. The effect of P-450 3A4 inducers (eg rifampicin or phenytoin) on cerivastatin pharmacokinetics was unknown. Possible interaction with other substrates of the isoenzyme was unknown but should be considered for other drugs with a narrow therapeutic index. No clinically significant effects were seen in a range of other interaction studies with drugs commonly prescribed in hypercholesterolaemic patients (for example warfarin, digoxin, antacids, cimetidine).

The Lipitor (atorvastatin) SPC stated that atorvastatin was metabolised by P-450 3A4 indicating the possibility of an interaction with medicines also metabolised by this isoenzyme. In clinical studies where Lipitor was administered with antihypertensives (including ACE inhibitors, beta blockers, calcium channel antagonists and diuretics) or hypoglycaemic agents, no clinically significant interactions were seen. Caution was also advised when Lipitor was administered with inhibitors of P-450 3A4 (eg macrolide antibiotics and azole antifungals). The effect of inducers of P-450 3A4 on Lipitor was unknown.

The Panel considered that the letter was only partly correct with regard to potential interactions due to cytochrome P-450 interactions. Each of the SPCs for atorvastatin, cerivastatin, and simvastatin referred to cytochrome P-450 3A4. The fluvastatin SPC referred to P-450 CYP2C and this was not mentioned in the letter.

The Panel considered that the impression from the letter about potential interactions was misleading in the light of the detailed information in the SPCs. No mention was made of the clinical significance of any of the interactions. Some were just theoretical possibilities. Readers would not be able to judge the significance of the interactions from the letter. It further noted the respondents' view that interactions with the statins metabolised by cytochrome P-450 were rare. The Panel considered that the letter was misleading with respect to potential interactions and ruled a breach of Clause 7.2 of the Code. The letter was disparaging of the other statins and a breach of Clause 8.1 of the Code was also ruled.

Complaint received **20 October 1998**

Case completed **6 January 1999**

CASE AUTH/781/10/98 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER v ASTRA

Plendil journal advertisement

A general practitioner complained about a journal advertisement for Plendil (felodipine), a calcium antagonist, issued by Astra. The advertisement discussed the use of felodipine in the HOT (hypertension optimal treatment) international study. The headline stated "One of the world's biggest hypertension trials used Plendil. But Plendil wasn't on trial". The advertisement also stated that "Plendil has already proved itself, in over 40 studies" and "For Plendil, sentences of acclaim are being passed around the World" and referred to Plendil as being an effective, reliable, high value antihypertensive.

The complainant said that he was concerned about the advertisement, particularly in view of two independent articles in Prescriber, one of which stated that the results of the study were rather disappointing. The advertisement stated that Plendil had proved itself. Proved what? Proved was a strong word to use. The terms "reliable" and "high value" were ambiguous. The statement ".....sentences of acclaim are being passed around the world" seemed surprising as there had recently been concern about this group of medicines. The article previously referred to only stated that "this provides some reassurance of the value and safety of this embattled drug class". The complainant alleged that the claims for Plendil were misleading, if not inaccurate, and exaggerated. A false impression was given of Plendil's efficacy.

The Panel noted that the advertisement stated that Plendil had already proved itself in over 40 studies. In order to gain a product licence, efficacy, quality and safety would have had to be demonstrated. The Panel did not agree that the claim was misleading or exaggerated as alleged. There was data from over 40 studies. In addition, nearly 80% of patients in the HOT study remained on Plendil throughout the four year trial. The Panel did not accept that the advertisement gave a false impression of the efficacy of Plendil and no breach of the Code was ruled. The advertisement referred to Plendil as being an effective, reliable, high value antihypertensive. The Panel noted the data regarding the safety of calcium antagonists in general and the data for Plendil. The Panel noted the definition of reliable as dependable, reputable, trusted and considered that the use of the word was not unacceptable. Plendil was not the least expensive calcium antagonist, but it was less expensive than a number of branded products. The Panel considered that in the context of the advertisement the words "reliable" and "high value" were not ambiguous as alleged. No breach of the Code was ruled. The Panel did not consider that the claim that "...sentences of acclaim are being passed around the world" was misleading, inaccurate or exaggerated. The data from the HOT study had generated widespread acknowledgement of the clinical impact of the study. The advertisement clearly stated that Plendil was not on trial and that the aim of the HOT study was to compare morbidity and mortality at different blood pressure levels. No breach of the Code was ruled.

A general practitioner complained about a two page journal advertisement (ref PLE 3619) for Plendil (felodipine) issued by Astra Pharmaceuticals Ltd. The advertisement appeared in Hospital Doctor, June 1998, and discussed the use of felodipine in the HOT (hypertension optimal treatment) international study. The headline, which occupied most of the advertisement, stated "One of the world's biggest hypertension trials used Plendil. But Plendil wasn't on trial." Felodipine was a calcium antagonist.

COMPLAINT

The complainant said that he was rather concerned to read the advertisement for Plendil, particularly in view of two independent articles in the journal Prescriber, copies of which he provided. The article by Dr G McInnes stated that the results of the study were rather disappointing.

The complainant said that the advertisement stated that Plendil was not on trial, since it had already proved itself. Proved what? This was misleading and exaggerated, since it implied a very good efficacy for Plendil. Proved was a strong word to use. Also, what did 'reliable' and 'high value' mean? These terms were ambiguous.

The last sentence of the advertisement stated "For Plendil, sentences of acclaim are being passed around the World". This also seemed surprising, since recently there had been a lot of concern about the safety of this group of medicines. Dr McInnes' article only stated that "this provides some reassurance of the value and safety of this embattled drug class." The claims for Plendil seemed to be therefore misleading, if not inaccurate, and exaggerated.

The complainant added that negative results had not been included in the advertisement which was misleading because it gave a false impression of the efficacy of Plendil.

RESPONSE

Astra stated the advertisement in question referred to the HOT study which was published in The Lancet in June 1998. This was a major international study in over 19,000 patients which set out to identify the optimum target diastolic blood pressure in hypertensive patients for reducing cardiovascular morbidity and mortality. The study results clearly demonstrated for the first time the optimum diastolic blood pressure for reducing morbidity and mortality in hypertensive patients, when treated with stepwise medication using Plendil as the baseline therapy. Since publication of the study there had been widespread acknowledgement of the clinical impact of the study findings.

The impact of the study had been such that the results were being used in the reappraisal of international and national hypertension guidelines with regard to what constituted optimum blood pressure lowering targets in hypertensive patients.

Astra noted that the complainant cited two independent articles in Prescriber as a cause for concern. Whilst not all of the issues on hypertension management were addressed by the HOT study, it was clear that both articles were supportive of the important positive results shown by the study. McInnes emphasised the important practical messages, as a result of the study, for the general practitioner in the management of their hypertensive patients. Such reviews were supported by numerous articles which had been published, since the results of the HOT study first became available, discussing the important implications for the management of hypertension. Copies of articles etc were provided by Astra.

Astra noted that the complainant stated that the use of the statement "Plendil has already proved itself" was misleading and exaggerated. Astra pointed out that the text of the advertisement further stated that Plendil had proven itself in over 40 studies. The Oxford Dictionary defined "to prove" as "to be found to be, demonstrate, establish, support". The statement in the advertisement referred to the fact that Plendil had proven itself in the treatment of hypertension. Plendil did have proven efficacy and safety in the treatment of hypertension as supported by numerous studies since the launch of the product, as well as by the product licence.

Astra noted that the complainant questioned what was meant by the terms "reliable" and "high value" and stated that these terms were ambiguous. The Oxford Dictionary definition of "reliable" included "dependable, reputable, trusted". "Reliable" was used to refer to the fact that in the treatment of hypertension Plendil could be relied on as it had demonstrated efficacy and safety in this disease area, as supported by clinical studies and its product licence. Plendil was of "high value" from both a clinical and cost-effectiveness viewpoint. Plendil was over 30% cheaper than the leading calcium antagonist in its class. As a result it represented value to customers with regard to prescribing costs. As a result of Plendil's demonstrated efficacy and tolerability, it also represented high value to the customer in the clinical setting for the treatment of hypertension.

Astra noted that the complainant referred to the concern about the safety of this group of medicines. Concern regarding this class of medicines was raised as a result of observational studies involving short-acting calcium antagonists, principally nifedipine, suggesting a possible increase in cardiovascular mortality. As a result of such concerns the World Health Organization and International Society of Hypertension formed an *ad hoc* committee to review all the data on the safety of all classes of calcium antagonists in both randomized clinical trials and observational studies. The results of their findings were published in 1997 and their conclusions clearly showed there was no evidence of harm with any class of calcium antagonist. Such results were further supported by extensive evidence on the safety of the class of long-acting dihydropyridine calcium antagonists to which Plendil belonged and was further supported by the results of the HOT study.

In addition to the WHO/International Society of Hypertension review there was specific information on Plendil from Astra's safety database.

In the Astra Plendil (felodipine) research file, which included all randomized controlled studies with felodipine, there was no suicidal attempt or suicide in any patients treated with felodipine (n>8000), or in the placebo group (n>2000). This was also not evident in the patients who received comparator products (n>4000).

In post marketing studies (PMS), including 60,827 patients who had been exposed, which was over 8,681 patients years, one patient was reported to have committed suicide. This case came from a German PMS study. One suicide case in 8,681 patient years was about one third of what could be expected in the normal population.

In the HOT study including 18,790 hypertensive patients, exposed during approximately 72,000 patient years, 8 suicides had been reported. Again this figure was in accordance to one third of what could be expected in the normal population.

In the HOT study quality of life results had been investigated. Both before treatment and after six months 781 patients answered two questionnaires, the Psychological Well Being Index and the Subjective Symptoms Assessment Profile. The lower the blood pressure ie DBP <85 and <80mmHg achieved, the greater improvement in well-being ($p<0.05$). Anxiety, depression, and well-being improved significantly from baseline to after six months treatment. (Wiklund *et al* 1997).

A review concluded in March 1998, showed that there was no suicide case report from the market since felodipine had been available.

Thus in the presently available clinical documentation of Plendil there had not been any suggestion of an untoward effect with regard to suicidal risk.

Safety was closely and continuously monitored in all clinical studies with felodipine. In a recent analysis of the complete safety data from all clinical studies with Plendil, which involved over 100,000 patients, there was no indication of untoward effects with regard to major clinical events.

The statement in the advertisement "sentences of acclaim are being passed around the World" clearly referred to the HOT study and the results demonstrated with Plendil as baseline medication. Therefore, Astra did not agree that such a statement in the light of the available evidence, the position of the WHO and International Society of Hypertension and the results of the HOT study was misleading, inaccurate or exaggerated.

Astra noted that the complainant stated that negative results had not been included in the advertisement. Plendil had been shown to be an effective antihypertensive in numerous trials. The advertisement gave a balanced representation of the HOT study. It would not be possible to present all the results of such a study. There had been considerable correspondence in the medical press on the results of the study and any negative comments which had been raised had been clearly addressed by the authors. In view of the important results demonstrated by the HOT study, Astra did not agree that the advertisement was misleading and that it gave a false impression of the efficacy of Plendil.

In summary, Astra believed that the advertisement was a

fair and balanced representation of the HOT study and the product Plendil. Astra believed that it had provided appropriate clarification on the issues raised by the complainant.

PANEL RULING

The Panel noted the headline claim in the advertisement "One of the world's biggest hypertension trials used Plendil. But Plendil wasn't on trial". The advertisement stated that "Plendil has already proved itself, in over 40 studies" and referred to the study which aimed to compare morbidity and mortality at different blood pressure levels. The advertisement finished with the statement "Since 1992, the H.O.T. study verdict has been eagerly awaited. For Plendil, sentences of acclaim are being passed around the World".

The study was published in The Lancet in June 1998. The principal sponsor was Astra AB Sweden. The principal result demonstrated the benefits of lowering blood pressure in patients with hypertension to 140mmHg systolic and 85mmHg diastolic or lower. Felodipine at 5mg once daily was given to all patients. Additional therapy and dose increments in four further steps were prescribed to reach the randomised target blood pressure. Angiotensin converting enzyme (ACE) inhibitors or beta blockers were added at step two and dose titrations were used at step three (felodipine 10mg once daily) or step four (doubling the dose of either the ACE inhibitor of the beta blocker). There was the possibility of adding a diuretic at step five.

The Panel noted that the article in Prescriber stated that the main results of the HOT study were rather disappointing. The trend for the greatest risk reduction in those patients randomised to the lowest band of target diastolic blood pressure (≤80mmHg) was not significant. This was mainly because the event rate was 75% of that expected. The author stated that the study was probably underpowered. The low event rate probably reflected the reluctance of clinicians to enrol truly high risk, particularly elderly, patients in clinical trials as well as the general excellence of blood pressure control. Most patients received combination therapy and there was no placebo control. It was impossible to attribute the large falls in blood pressure or the low event rate to any particular medicine. The results offered some reassurance of the value and safety of felodipine.

The Panel noted that the advertisement stated that Plendil had already proved itself in over 40 studies. The Panel noted that in order to gain a product licence, efficacy, quality and safety would have had to be demonstrated. The Panel did not agree that the claim was misleading or exaggerated as alleged. The Panel noted the complainant's comment that negative results had not been included in the advertisement. The complainant had not provided any further details. The Panel noted that there was data from over 40 studies. In addition nearly 80% of patients in the HOT study remained on Plendil throughout the four year trial. The Panel did not accept that the advertisement gave a false impression of the efficacy of Plendil. No breach of the Code was ruled.

The Panel noted that the advertisement referred to Plendil as being effective, reliable, high value antihypertensive. The Panel noted the data regarding the safety of calcium antagonists in general and the data for Plendil. The Panel noted the definition of reliable as dependable, reputable, trusted and considered that the use of the word was not unacceptable. The Panel noted the submission from Astra that Plendil was over 30% cheaper than the leading calcium antagonist in the class and as a result of this it represented value to customers with regard to prescribing costs. The Panel noted that Plendil was not the least expensive calcium antagonist but it was less expensive than a number of branded products. The Panel considered that in the context of the advertisement the words "reliable" and "high value" were not ambiguous as alleged. No breach of the Code was ruled.

The Panel did not consider that the final sentence in the advertisement copy that "...sentences of acclaim are being passed around the World" was misleading, inaccurate or exaggerated. The data from the HOT study had generated widespread acknowledgement of the clinical impact of the study. The advertisement clearly stated that Plendil was not on trial and that the aim of the HOT study was to compare morbidity and mortality at different blood pressure levels. No breach of the Code was ruled.

Complaint received **23 October 1998**

Case completed **18 January 1999**

CASE AUTH/782/10/98

DOCTOR v PFIZER

Meeting on former Royal Yacht

A doctor sent in an article which had appeared in The Times on 24 October 1998. The article was entitled "Viagra makers turn Britannia into love boat" and referred to Pfizer's plans to invite doctors to attend a Viagra (sildenafil) conference and dinner on board the former Royal Yacht. The complainant said that if this was true, such a meeting and the publicity which it had attracted brought discredit upon the industry and was in breach of Clause 2 of the Code. Further, the hospitality proposed was not secondary to the purpose of the meeting.

The Panel noted that the Code did not prevent companies from holding meetings for UK health professionals at attractive venues, but the programme should attract delegates and not the venue. According to the programme delegates were to arrive at the meeting from 6.30pm onwards, with the educational programme starting at 7.15pm. There were to be four short presentations on various aspects of erectile dysfunction given by a physician, a surgeon, a psychiatrist and finally by the chairman who was a general practitioner. This was to be followed by forty minutes of questions and answers. The meeting was to end with a buffet at 9.15pm.

The Panel expressed concern that the arrangements for the meeting had been such as to attract media attention. In the Panel's view such attention might reasonably have been expected given the venue and the medicine being promoted. The newspaper article was sub-titled "Doctors treated to promotional bash on the former Royal Yacht..." and stated that Pfizer's meeting was the third private function to be held on board Britannia which had recently opened as a tourist attraction. In the Panel's view, the impression of the pharmaceutical industry as a whole created by such coverage was not good. The Panel noted that once Pfizer had become aware that its arrangements for the meeting had attracted a lot of media attention, and on receipt of notification of the complaint, the company had moved the meeting to a less high profile venue. The Panel considered that, notwithstanding the change of venue and the reduction in the level of hospitality, the impression created by the overall arrangements for the meeting to be held on the former Royal Yacht was unacceptable. In the Panel's view the proposed hospitality was not secondary to the main purpose of the meeting and nor was it appropriate for pharmaceutical companies to hold meetings at such venues. A breach of the Code was ruled. The Panel considered that as the educational content of the meeting was not unreasonable there was no breach of Clause 2.

A doctor complained about an article which appeared in The Times, on Saturday, 24 October 1998. The article was entitled "Viagra makers turn Britannia into love boat" and referred to Pfizer Limited's plans to invite doctors to attend a Viagra (sildenafil) conference and dinner on board the former Royal Yacht. The meeting had been planned for Thursday, 29 October 1998.

COMPLAINT

The complainant stated that if the article was true, he considered that the event breached Clause 2 of the Code, as such a meeting and the publicity which it had attracted brought discredit to the pharmaceutical industry. In addition, the hospitality proposed was not secondary to the purpose of the meeting, in breach of Clause 19.

RESPONSE

Pfizer stated that following the licensing of Viagra, a number of launch meetings were being held around the country to inform general practitioners about the product and to educate them on the subject of erectile dysfunction generally. These meetings were organised by representatives in their local area working with interested GPs and specialists. The conference which was the subject of this complaint was for GPs in the central belt of Scotland. Four hundred and sixty GPs and thirty two specialists were invited to attend the meeting. The former Royal Yacht Britannia was chosen as the venue because it was an appropriate size for the expected audience and in a convenient location (Leith Docks in Edinburgh). Pfizer submitted that the venue, being slightly unusual, would also make the event memorable. Since the decommissioning of the yacht, it had been opened as a conference venue.

Beginning on 22 October, a week before the meeting and continuing over the preceding weekend, the meeting had attracted a lot of media comment, apparently because it was being held at a new venue with an interesting history, in addition to the general media interest in Viagra. In Pfizer's view this focus of attention was inappropriate for an educational meeting on a serious medical subject, and a condition which caused considerable distress to sufferers and their partners. Wishing to avoid any resulting embarrassment to the doctors attending the conference, and bearing in mind this complaint, Pfizer, took the decision to change the venue to Heriot-Watt University. Delegates were informed of this individually by telephone.

The conference therefore took place with exactly the same programme as originally planned, albeit at a different venue. The two-hour meeting included presentations from leading specialists in the fields of diabetes, urology and psychiatry, together with a general practice perspective from the Chairman, a local GP. A copy of the programme was provided. The conference received post graduate education allowance (PGEA) approval for its educational content. The hospitality provided consisted of tea, coffee and biscuits on arrival, and later a fork buffet.

In relation to the allegation that the company had breached Clause 19 of the Code, Pfizer submitted that if

this related to the choice of venue being the former Royal Yacht and hospitality in that regard, then there was no case to answer as no meeting was held there and no such hospitality was in fact provided. If on the other hand the complaint related to the meeting as held at Heriot-Watt University, then Pfizer submitted that no breach of the Code was committed as the hospitality offered was secondary to the purpose of the meeting, appropriate in level and not out of proportion to the occasion. It would be reasonable to expect the delegates to adopt the same level of hospitality when paying for themselves.

Pfizer provided details of the cost involved at each of the two venues and a list of attendees.

With regard to the very serious allegation that the company also breached Clause 2 of the Code, Pfizer submitted that such particular censure was not appropriate in the circumstances. Given that, in the company's view, no breach of Clause 19 was committed, and that the media attention the conference received was outside Pfizer's control, the company considered that it took the most responsible course of action possible in changing the venue. Therefore, Pfizer could not be said to have brought the pharmaceutical industry into disrepute.

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 attractive venues. The supplementary information to Clause 19.1 stated that the arrangements for any meeting must be kept in mind. In the Panel's view the programme should attract delegates and not the venue.

The Panel noted that doctors from the central belt of Scotland had been invited to attend the meeting. The letter of invitation made no mention of the proposed venue. Information about the venue was provided on the programme which was attached to the invitation together with a form for participants to indicate priority needs for the focus of the meeting. The Panel noted that mention of the venue was straightforward and factual. According to the programme delegates were to arrive at the meeting from 6.30pm onwards, with the educational programme starting at 7.15pm. There were to be four short presentations on various aspects of erectile dysfunction given by a physician, a surgeon, a psychiatrist and finally by the Chairman who was a GP. This was followed by forty minutes of questions and answers. The meeting ended with a buffet at 9.15pm.

The Panel expressed concern that the arrangements for a meeting had been such as to attract media attention. In the Panel's view such attention might have been reasonably expected given the venue and the medicine being promoted. The newspaper article was sub-titled "Doctors treated to promotional bash on the former Royal Yacht...." and stated that Pfizer's meeting was the third private function to be held on board Britannia which had recently opened as a tourist attraction. In the Panel's view, the impression of the pharmaceutical industry as a whole created by such coverage was not good. The Panel noted that once Pfizer had become aware that its arrangements for the meeting had attracted a lot of media attention, and on receipt of notification of this complaint, the company had moved the meeting to a less high profile venue. According to the documents provided by Pfizer, 65 healthcare professionals attended the meeting. The Panel noted that the buffet provided at the meeting which actually took place was more modest than that which appeared to have been planned on board Britannia.

The Panel considered that, not withstanding the change of venue and the reduction in the level of hospitality, the impression created by the overall arrangements for the meeting to be held on the former Royal Yacht was unacceptable. In the Panel's view the proposed hospitality was not secondary to the main purpose of the meeting and nor was it appropriate for pharmaceutical companies to hold meetings at such venues. A breach of Clause 19.1 was ruled.

The Panel considered that as the educational content of the meeting was not unreasonable there was no breach of Clause 2 and ruled accordingly.

Complaint received **26 October 1998**

Case completed **18 December 1998**

CASE AUTH/784/10/98

SHIRE v PROCTER & GAMBLE

Cacit D3 journal advertisement

Shire complained about a journal advertisement for Cacit D3 issued by Procter & Gamble. Cacit D3 was presented as effervescent granules of calcium carbonate and cholecalciferol (vitamin D_3). Citric acid was included as an excipient. During dissolution the calcium salt was transformed into calcium citrate. Shire marketed Calcichew D_3, a chewable tablet of calcium carbonate and cholecalciferol. The advertisement addressed issues relating to the absorption of calcium.

Shire alleged that the claim "Calcium citrate is more than twice as effective as calcium carbonate in the prevention of bone resorption", which was referenced to Talbot *et al*, was based on extremely weak, indirect evidence taken from an abstract of very poor quality. A better quality publication, Deroisy *et al*, gave a result inconsistent with the claim. Shire said that the claim referred to calcium salts without vitamin D_3 whereas the remainder of the advertisement referred to calcium salt/vitamin D combinations. The Talbot study related to calcium citrate, not the calcium carbonate/citric acid formulation in Cacit D3. There were a number of unsatisfactory aspects of the study which involved only seven days' treatment, which was unacceptably short for long term therapy such a calcium supplementation.

In the Panel's view, the Talbot study was more relevant to the clinical situation than the Deroisy study. The Panel noted that while the Talbot study had involved patients with post menopausal osteoporosis, the duration of the study had only been seven days. The patients were not vitamin D deficient. In addition the study medication had not been Cacit D3, the subject of the advertisement in question. The Panel considered that the claim "Calcium citrate is more than twice as effective as calcium carbonate in the prevention of bone resorption" gave insufficient information with regard to the study to which it was referenced to allow readers to judge its significance. The Panel considered that the claim was misleading and ruled a breach of the Code.

Shire said that the juxtaposition of the claim "At just 27p/day, Cacit D3 has a lower cost than branded chewable calcium carbonate and vitamin D3" and the claim at issue above appeared to imply that the appropriate daily dosage of calcium for Cacit D3 was half that of branded chewable calcium carbonate/vitamin D_3 (Calcichew D_3 Forte). The claim should have stated what was meant by the term "appropriate daily dose". If the correct equivalent doses (in terms of the same calcium and vitamin D_3 doses) were employed, then the claim was simply incorrect. Shire alleged that the claim was inaccurate and misleading.

The Panel noted that the dose of Cacit D3 was one or two sachets daily and this was given in the prescribing information in the advertisement. The cost of each sachet was 27 pence. The claim in question was thus based on a dose of one sachet of Cacit D3. The Panel noted that the claim was asterisked to the statement "At appropriate daily dosage". There was no further information to allow the reader to determine what the appropriate daily dosage might be of either medicine, nor to determine that the 27 pence per day referred to only one sachet of Cacit D3. The Panel noted the submission that the average daily dose of Cacit D3 prescribed was 1.1 sachets. The Panel considered that the claim was misleading and a breach of the Code was ruled.

Shire Pharmaceuticals Ltd complained about an advertisement for Cacit D3 (ref CD976), issued by Procter & Gamble Pharmaceutical UK, Limited, which had appeared in GP, 2 October. Cacit D3 was presented as effervescent granules of calcium carbonate and cholecalciferol (vitamin D_3). Citric acid was included as an excipient. During dissolution the calcium salt was transformed into calcium citrate. Shire marketed Calcichew D_3, a chewable tablet of calcium carbonate and cholecalciferol. The advertisement addressed issues relating to the absorption of calcium. Two of the bullet points were alleged to breach the Code.

1 Claim "Calcium citrate is more than twice as effective as calcium carbonate in the prevention of bone resorption"

This was the second of the three bullet points and was referenced to a study by Talbot *et al* (1995).

COMPLAINT

Shire alleged that the claim was based on extremely weak, indirect evidence taken from an abstract of very poor quality. Furthermore, one other (much better quality) relevant publication had not been considered in order to construct a balanced comparison. Shire made a number of specific comments.

i The claim referred only to calcium salts without vitamin D_3 (as did the publication). The claims in the remainder of the advertisement referred to the calcium salt/vitamin D combinations. This use of different products (single and combined) and the implied extrapolation from one to the other was misleading.

ii The Talbot *et al* publication claimed results using calcium citrate, not the effervescent calcium carbonate/citric acid formulation in Cacit D3. There was no statement in the publication as to how the medications were administered (eg chewable tablets, effervescent granules etc). Therefore the comparisons were not fair and were misleading.

iii The Talbot *et al* trial was not randomised and double-blind and there was no indication how the treatment arms were selected. No baseline (demographic) data were given for patients on the different treatment arms and there was no evidence that the different arms were matched, or that the different groups were equally compliant in taking the medication. Shire referred to Figure 2 in the Talbot abstract which was entitled Pyridinoline/creatinine (nmol/mmol) and noted one "basal" level was represented for all patients. This was extremely dubious; one would expect differences between the two treatment arms. In addition, error bars in Figure 2 were only described in the positive direction and no substantiation of the statistical methods was given. Shire

noted that three years had elapsed since the abstract was presented; this was ample time for a full presentation of these results (with appropriate details) to have been published to substantiate the claims in the abstract.

iv There was an extrapolation from a result (of dubious reliability, as discussed above) involving a surrogate marker (pyridinoline/creatinine in urine) to a claim about bone resorption. The study involved only 7 days' treatment, which was unacceptably short for long-term therapy such as calcium supplementation. Only one marker (among several available) of bone resorption was cited. From the very limited surrogate data quoted, it was totally unacceptable to extrapolate quantitatively from a surrogate marker to bone resorption.

v A much better quality randomised, double-blind study (Deroisy *et al*) had not been considered in the advertisement. In this publication, the subjects acted as their own internal controls and changes in serum calcium and PTH levels were compared, following administration of a vehicle and five different calcium salts [including Orocal (calcium carbonate) and Cacit]. There was no significant difference between Orocal (calcium carbonate) and Cacit (given at the same calcium doses) in terms of serum calcium and PTH levels. This result was not consistent with the claim in question.

Shire alleged that the claim was misleading, not based on up-to-date evidence, inaccurate, unbalanced and unfair. A breach of Clause 7.2 was alleged.

RESPONSE

Procter & Gamble responded in turn to the specific points raised by Shire.

i Procter & Gamble noted that Shire had suggested that the use of a "single product" in the second bullet point, and "combined products" in the third bullet point, resulted in an "implied extrapolation from one to another" and that this was "misleading". Procter & Gamble considered that this was clearly incorrect.

While it was true that the Talbot study referred only to calcium citrate without vitamin D, it was not misleading to highlight more specifically one component of a therapy. From the argument presented by Shire, it appeared that it had not understood the reference used to support the claim of "more than twice as....". Procter & Gamble explained that Figure 2 in the Talbot abstract showed that the fall in pyridinoline levels versus baseline following a calcium citrate load was approximately 2.7 x that of the fall in pyridinoline with calcium carbonate. This was a highly significant difference ($P<0.0001$) in the reduction of bone resorption in a comparison between the two groups versus baseline. This provided the claim "calcium citrate is more than twice as effective as calcium carbonate in the prevention of bone resorption".

Procter & Gamble considered there was no implied or overt extrapolation from the second bullet point to the third (see v below). Hence, Procter & Gamble considered that the claims made in the second and third bullet points, were balanced and fair and not in breach of Clause 7.2 of the Code.

ii Procter & Gamble stated that when dissolving the contents of a sachet of Cacit D3, calcium citrate was formed as mentioned in the pharmacokinetics section of the summary of product characteristics (SPC). Patients taking Cacit D3 thus had an intake of calcium citrate as the active ingredient. Procter & Gamble therefore correctly referred to it and felt that this was not unfair or misleading. Talbot *et al* clearly stated that "Calcium supplements are available commercially" and they examined the "more popular preparations" in the study. Initially, they examined the "disintegration / dissolution" rate, and then the effects in post-menopausal women.

Therefore, Shire's assertion that there was no statement in the publication as to how the medications were administered was an incorrect one based on the following:-

- The abstract clearly stated that the same "more popular preparations" (Calcium - A, B, C, D) were used in the *in vitro* and *in vivo* studies.
- Three of the four products had calcium carbonate as the active ingredient.
- Rate of dissolution studies clearly indicated that the preparations were solids.

The details of the pharmaceutical form were not relevant given that results of the dissolution tests were significantly in favour of calcium citrate vs calcium carbonate ($p<0.001$). A full statement on the administration would not be expected within an abstract and would be applicable to a full publication. Therefore, the comparisons made were not misleading.

iii Procter & Gamble stated that with regard to the issue of non-randomisation, the study design was not indicated in the abstract, and Shire was making insupportable assumptions as to the nature of the study.

The abstract clearly indicated that these patients were "20 female patients, 60 ± 5 years of age, with postmenopausal osteoporosis". There was no evidence to suggest that the treatment arms were not matched, or that the groups were not equally compliant. Procter & Gamble did not accept that "one would expect" differences between two treatment arms that had been matched.

With regard to the presentation of error bars for column graphs, it was well known that statistical convention dictated that for a graph with a linear axis, the upper error bars only were indicated, as the magnitude of the error was symmetrical, and therefore the presentation of the lower error bar would interfere with the presentation of the column. The publication used was an abstract and as such would not be expected to have substantiation of a method of statistical analysis.

Substantiation of claims in a peer-reviewed journal was obviously the aim of any piece of research. However, persons involved in research were well aware of the vagaries and difficulties in getting acceptance for publication, even if the study design or data presented contributed to ensure that the paper submitted was of a high technical standard. Factors such as originality, topicality, other research submitted at the time would contribute to acceptance or not. As such, aspersions or implications cast by Shire on the technical quality of this data were grossly unfair.

For the above reasons, Procter & Gamble felt that the comparisons made were <u>not</u> inaccurate and unfair.

iv With regard to the reliability of the data, Procter & Gamble referred to all its answers to the previous point on the nature of the study. The company did not agree that the data presented in the Talbot paper was unreliable.

With regard to the use of pyridinoline as a surrogate marker and for the duration in question, Procter & Gamble believed that this was perfectly valid.

- With regard to the short duration of the study, investigators other than Talbot had also shown a decline in pyridinoline, and in as little as 4 hours after a calcium load. This was in contrast to markers of bone formation which were well recognised to have a more gradual decline in response to therapy.
- With regard to the acceptability of pyridinoline, there were a number of bone resorption markers that were universally accepted. These included urinary pyridinoline (and other pyridinium crosslinks of collagen, and collagen telopeptides), hydroxyproline and tartrate-resistant acid phosphatase (TRAP). Urinary pyridinoline was thought to represent an improvement over markers such as hydroxyproline because the assays available for these markers showed a more dynamic response to therapy and had less day to day variability.

Therefore, Procter & Gamble disagreed that the use of this bone resorption marker was "limited" or that the duration of the study was too short to derive any conclusions of the effects of a calcium load on bone resorption. In addition, it believed that there did not exist any later evidence to refute the suggestion that an oral dose of calcium citrate, when given to elderly post-menopausal women, reduced markers of bone resorption more than calcium carbonate.

Therefore, for the above reasons, Procter & Gamble considered that the claims it had made were accurate and did not mislead.

v While Procter & Gamble did not intend to question the quality of the Deroisy study, it would suggest that it was not of better quality than the Talbot study since the Talbot publication did not indicate the precise study design. Therefore, in the absence of this information, a comparison could not be made as to the quality of the study, and Shire was making an incorrect conclusion based on an insupportable assumption.

Procter & Gamble did consider the Deroisy study when researching data for the claim, but considered that it could not be used for the following reasons:

- The study involved normal healthy volunteers, and not osteoporotic patients. As per the supplementary information to Clause 7.2 of the Code, Procter & Gamble acknowledged that "particular care should be taken by companies in the use of data derived from *in vitro* studies, studies in healthy volunteers and in animals".
- The study involved young males, and not old female patients. The company again referred to the supplementary information to Clause 7.2.
- The Deroisy study looked at serum parathyroid hormone (PTH) and calcium, with the authors stating that "Decrease of serum PTH levels below the lower limit of the normal range needs to be confirmed as clinically relevant". In contrast, pyridinoline was widely accepted as a marker of bone resorption (as explained above in point iv).

The obvious inconsistency in the complaint strategy produced by Shire should be noted. In the first letter of complaint from Shire that was received by Procter & Gamble (dated 30 September 1998), Shire criticised the use of the Talbot study with a small number of patients. However, Shire was prepared to offer the study by Deroisy which had even fewer subjects (18 persons), as evidence to support its complaint.

As pointed out in its response to point iv above, to the best of its knowledge, Procter & Gamble believed that there did not exist any later evidence to refute the suggestion that an oral dose of calcium citrate, when given to elderly post-menopausal women, reduced markers of bone resorption more than calcium carbonate.

Procter & Gamble considered that the claims made were accurate, fair and provided up-to date information based on the above response.

PANEL RULING

The Panel noted from the SPC that Cacit D3 was indicated for the correction of vitamin D and calcium combined deficiency in elderly people. Cacit D3 might be used as an adjunct to specific therapy for osteoporosis, in patients with either established vitamin D and calcium combined deficiencies or in those patients at high risk of needing such therapeutic supplements. Cacit D3 was a fixed combination of calcium carbonate and vitamin D_3.

The Panel noted that the study by Talbot *et al* compared the *in vivo* effect of calcium carbonate and calcium citrate on bone resorption in 20 female patients, 60 ± 5 years of age, with postmenopausal osteoporosis and without vitamin D deficiency. Efficacy was evaluated after 7 days' treatment by means of indirect markers for bone resorption, urinary pyridinoline and creatinine. Results showed that, compared with calcium carbonate, calcium citrate significantly decreased bone resorption ($p<0.001$).

The Panel noted that the study by Deroisy *et al* evaluated and compared the changes in serum calcium and parathyroid hormone (PTH) circulating levels induced by the oral absorption of various preparations of calcium, over a 6-hour period of follow-up. Preparations included calcium carbonate (Orocal) and calcium citrate (Cacit). The study population was eighteen healthy male volunteers. All the tested preparations induced a significant increase in serum calcium and a significant decrease in serum PTH. The authors, however, stated that there might be age and gender differences in calcium absorption and their results might be difficult to extrapolate to postmenopausal women. In addition further studies would be needed to assess whether the effects were sustained during long-term administration.

In the Panel's view the Talbot study was more relevant to the clinical situation than the Deroisy study. The Panel noted that while the Talbot study had involved patients with post menopausal osteoporosis the duration of the study had only been seven days. The patients were not vitamin D deficient. In addition the study medication had

not been Cacit D3, the subject of the advertisement in question. The Panel considered that the claim "Calcium citrate is more than twice as effective as calcium carbonate in the prevention of bone resorption" gave insufficient information with regard to the study to which it was referenced to allow readers to judge its significance.

The Panel considered that the claim was misleading and ruled a breach of Clause 7.2 of the Code.

2 Claim "At just 27p/day, Cacit D3 has a lower cost then branded chewable calcium carbonate and vitamin D3."

The claim appeared as the third of the three bullet points immediately below the claim at issue in point 1 above and was asterisked to a statement which read "At appropriate daily dosage".

COMPLAINT

Shire stated that the juxtaposition of this claim and the claim at issue in point 1 above appeared to imply that the appropriate daily dosage of calcium for Cacit D3 was half that of branded chewable calcium carbonate/vitamin D_3 (Calcichew D_3 Forte).

Shire believed that this implication was incorrect for the reasons stated in point 1 above regarding the inadequacy of the Talbot *et al* abstract.

The claim should have stated what was meant by the term "appropriate daily dose". If the correct equivalent doses (in terms of the same calcium and vitamin D_3 doses) were employed, then the claim in bullet point three was simply incorrect.

Shire alleged that the claim was inaccurate and misleading in breach of Clause 7.2 of the Code.

RESPONSE

Procter & Gamble strongly disagreed with Shire's assertion that there was an implication that the appropriate daily dosage was half that of branded chewable calcium carbonate/ vitamin D_3. The use of the words "at appropriate daily dosage" defined the need for supplementation to a "suitable" daily dosage.

Therefore, for the relevant indications, the "appropriate" dose required by any patient had been assumed to be that which returned a deficient patient to a level on a par with a normal reference range. In the UK, a figure of 1500mg as a suggested daily calcium intake had been used by some experts, based on guidance developed from the American National Institute of Health (NIH) Consensus Development Panel on Optimal Calcium Intake, 1994.

However, there had been more recent recommendations issued by the Food and Nutrition Board (FNB) of the National Academy of Sciences in Washington, USA. The FNB had adopted Dietary Reference Intakes (DRI's) as a new approach to providing quantitative estimates of nutrient intakes which were composed of Adequate Intake (AI) levels, Recommended Daily Amounts (RDA), Upper Intake Levels (UL) and Estimated Average Requirements (EAR). Therefore, for adult males and females over the age of 51, the AI levels for calcium published by the FNB were equivalent to 1200mg/day and 400-600 IU of vitamin D. The AI was defined as a level of consumption that would meet the needs of all individuals in a particular group (and might actually exceed the RDA). It was therefore by definition higher than the actual needs of a large proportion of people within that particular group.

Based on a large census study, the actual calcium intakes of UK patients were estimated at 940mg for men and 730mg for women and 120 IU of vitamin D. Therefore, the vast majority of elderly patients would have their intake boosted to this AI level with a single sachet of Cacit D3, providing 500mg of elemental calcium and 400 IU of vitamin D. Also, the most up-to-date medical marketing data available indicated that 73% of all Cacit D3 prescriptions were for a single sachet per day and that the average daily dose of Cacit D3 prescribed was 1.1 sachets.

Procter & Gamble stated that comparing the cost of 1 sachet of Cacit D3 against 1 tablet of branded chewable calcium carbonate and vitamin D would be logical but only valid and in adherence to the Code if a single tablet of branded chewable calcium carbonate and vitamin D were both licensed at that dose for the same indication, which was not the case. Therefore as a correct comparison based on the equivalent dosage requirement for the same indication, Procter & Gamble had adhered to the Code and compared the appropriate dosage of Cacit D3 (1 sachet) versus the licensed dosage of branded chewable calcium carbonate and vitamin D supplements (2 tablets), as opposed to the non-licensed single tablet dose.

Procter & Gamble believed that it had made a balanced, fair, objective price comparison as per Clause 7.2 of the Code. Therefore, in accordance with the supplementary information in Clause 7.2, the company considered that these comparisons were "made on the basis of the equivalent dosage requirement for the same indications".

PANEL RULING

The Panel noted that the dose of Cacit D3 was one or two sachets daily and this was given in the prescribing information in the advertisement. The cost of each sachet was 27 pence. The claim in question was thus based on a dose of one sachet of Cacit D3 daily. The Panel noted that the claim was asterisked to the statement "At appropriate daily dosage." There was no further information to allow the reader to determine what the appropriate daily dosage might be of either medicine nor to determine that the 27 pence per day referred to only one sachet of Cacit D3. The Panel noted the submission that the average daily dose of Cacit D3 prescribed was 1.1 sachets. The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

Complaint received **29 October 1998**

Case completed **25 January 1999**

GENERAL PRACTITIONER v SERVIER

Natrilix SR leaflet

A general practitioner complained about a leaflet relating to Natrilix SR (indapamide 1.5mg) which had been issued by Servier. The front page, entitled "Morbidity and Mortality in very elderly hypertensives", was labelled "Fact Sheet" and gave details of the HYVET study (hypertension in the very elderly trial) in which indapamide 1.5mg was the active treatment. The primary objective of the study was a 35% decrease in stroke. The secondary objectives were a 60% reduction in stroke mortality, a 50% reduction in cardiac mortality, a 35% reduction in cardiovascular mortality and a 25% reduction in total mortality. The start date was November 1998 and the finish date November 2003. A footnote stated that the study was powered to detect the objectives at 1% level of significance. The two inside pages explained the rationale for choosing to use Natrilix SR in the HYVET study while the back page featured a cost comparison chart and prescribing information.

The complainant was concerned that with a brief glance at the material one might assume that the trial was completed and that the figures represented trial results. It was most unusual to present data in this way. If one were to describe a new trial then one would usually describe the power of the trial, ie the minimum difference the trial had been designed to detect. The complainant alleged that the material might be deliberately misleading.

The Panel examined the layout and content of the relevant page. The Panel considered that as the primary and secondary objectives of the HYVET study were clearly and prominently labelled as such, and the start and finish dates of the trial were provided, the page was not misleading as alleged. No breach of the Code was ruled.

A general practitioner complained about a four page leaflet relating to Natrilix SR (indapamide 1.5mg) produced by Servier Laboratories Ltd which had been left at the surgery. The first page, entitled "Morbidity and Mortality in very elderly hypertensives" was labelled "Fact Sheet" and gave details of the design and objectives of the HYVET study (hypertension in the very elderly trial). It was stated that the active treatment in this study was indapamide 1.5mg. The primary objective of the study was a 35% decrease in stroke. The secondary objectives were a 60% reduction in stroke mortality, a 50% reduction in cardiac mortality, a 35% reduction in cardiovascular mortality and a 25% reduction in total mortality. The list of objectives was followed by the start date, November 1998, and the finish date, November 2003. A footnote appeared at the bottom of the page which stated that the study was powered to detect the objectives at 1% level of significance. The two inside pages explained the rationale for choosing to use Natrilix SR in the HYVET study while the back page featured a cost comparison chart and the prescribing information.

COMPLAINT

The complainant stated that the front cover (page 1) of the leaflet was a fact sheet - "Morbidity and Mortality in very elderly hypertensives" and then a description of a trial with some suggested percentage reductions in stroke and mortality.

The complainant was concerned that with a brief glance at the material one might assume that the trial was completed and that the figures represented trial results. As could be seen at the bottom of the page the start date of the five year trial was November 1998. It was most unusual to present data in this way. If one were to describe a new trial then one would usually describe the power of the trial ie the minimum difference the trial had been designed to detect.

The complainant alleged that the material might be deliberately misleading.

RESPONSE

Servier said that it did not consider that this piece was misleading and refuted most strongly the suggestion that it might be deliberately so.

This leaflet was distributed to general practitioners by Servier's representatives. It was usually an integral part of the representative's call, being referred to during the detail and then left with the general practitioner, but Servier recognised that the piece must also be capable of standing alone and addressed the complaint in that context.

The complaint related to page 1 of the leaflet, a fact sheet which gave the main features of the HYVET study. This was a major hypertension trial addressing an as yet unanswered question, namely the benefit of blood pressure reduction in patients over the age of 80 years. The increasing numbers of very elderly patients and the prevalence of hypertension in this age group made this a very relevant issue for the general practitioner. The aims of the HYVET study were recently reviewed for a general practitioner audience by Beckett *et al* (1998) in Prescriber.

Servier had not, at any time, had any intention to mislead by suggesting that the trial was complete. The start date and finish date were clearly given - November 1998 and November 2003.

In Servier's view it was very clear that the percent reductions were objectives and not results. The figures were given under a bold heading "Objectives". These figures were the minimum differences which the trial had been designed to detect and the power of the trial was explained in the footnote. (This appeared to be exactly what the complainant suggested would be a usual description for a new trial.)

Additionally the page did not include any brand name or logo for Natrilix SR, the only relevant mention being the fourth bullet point "active treatment: inadapamide 1.5mg" which appeared under the heading "Design". This was in the same type size as all other information on the fact sheet, including the start and finish date.

PANEL RULING

The Panel examined the layout and content of the relevant page of the leaflet. The Panel considered that as the primary and secondary objectives of the HYVET study were clearly and prominently labelled as such, and the start and finish dates of the trial were provided, the page was not misleading as alleged. No breach of Clause 7.2 was ruled.

During its consideration of this case, the Panel noted that Natrilix was licensed for the treatment of hypertension. The Panel considered that the list of primary and secondary objectives gave the impression that Natrilix was licensed to reduce stroke, stroke mortality, cardiac mortality and cardiovascular mortality, contrary to Clause 3.2 of the Code. The Panel decided that this matter should be taken up with Servier under Paragraph 16 of the Constitution and Procedure.

Complaint received **4 November 1998**

Case completed **14 January 1999**

CASE AUTH/793/11/98 *NO BREACH OF THE CODE*

ALCON v ALLERGAN

Alphagan journal advertisement

Alcon complained about a journal advertisement for Alphagan (brimonidine tartrate ophthalmic solution 0.2%) issued by Allergan. The advertisement was headed "Think Alphagan for long term IOP [intraocular pressure] control with a safety profile you can trust". Beneath the heading two bullet points discussed the efficacy and safety profile of the product and a third stated "Visual fields preserved – visual fields remained unchanged or improved in 95% of patients after 3 years".

Alcon alleged that the advertisement was inconsistent with Alphagan's marketing authorization and its summary of product characteristics (SPC). The SPC for Alphagan made no mention of visual field preservation.

The Panel noted that the SPC for Alphagan stated that it might be used as monotherapy for the lowering of intraocular pressure in patients with open angle glaucoma or ocular hypertension who were known or thought likely to be intolerant of topical betablocker therapy and/or in whom topical betablocker therapy was contra-indicated.

The Panel noted the layout and content of the advertisement. The indication for long term IOP control appeared as a heading followed by three stab points. The Panel noted that glaucoma was characterised by an increase in IOP which caused changes in the optic disc and typical defects in the field of vision. The Panel noted that the preservation of visual fields was a benefit of IOP control in patients with glaucoma. The Panel considered that on balance the claim referred to the feature of controlling IOP and was not a claim for an unlicensed indication. No breach of the Code was ruled.

Alcon Laboratories UK Limited complained about an advertisement (ref ACA 074/98) for Alphagan (brimonidine tartrate ophthalmic solution 0.2%) issued by Allergan Ltd which had appeared in the ophthalmic press, including Eye, October 1998. Alphagan was licensed for the treatment of glaucoma. The advertisement drew attention to some new three year data and was headed "Think Alphagan for long term IOP [intraocular pressure] control with a safety profile you can trust". Beneath the heading two bullet points discussed the efficacy and safety profile of the product. A third bullet point stated "Visual fields preserved - visual fields remained unchanged or improved in 95% of patients after 3 years".

COMPLAINT

Alcon alleged that the advertisement breached Clause 3.2 of the Code which stated that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics (SPC) or data sheet. The most recent Alphagan SPC made no mention of visual field preservation.

RESPONSE

Allergan explained that glaucoma was a disease of the eye which was usually characterised by an increase in intraocular pressure which caused pathological changes in the optic disc and typical defects in the field of vision. There were several assessments made by ophthalmologists as a diagnosis of glaucoma and during treatment in order to assess the efficacy of any treatment. These included; measurement of intraocular pressure, cup/disc ratio (cup became progressively larger in glaucoma), visual function - as glaucoma could cause contraction of visual field which ultimately resulted in tunnel vision.

Allergan pointed out that the statement in question "Visual fields preserved - visual fields remained unchanged or improved in 95% of patients after 3 years"

was referenced to an ongoing study which had reached three years. 94 patients were enrolled into this parallel group study of patients with open angle glaucoma or ocular hypertension. Patients were randomised to receive brimonidine 0.2% or timolol 0.5% and were seen at intervals of three months during this third year. Measurements of IOP and visual field assessments were made. It was concluded that brimonidine 0.2% was as effective as timolol in reducing IOP and that the efficacy of brimonidine had not lessened over the three years. Additionally, it was shown that visual fields remained unchanged or improved in 95% of the brimonidine treated patients.

The statement on visual fields in the advertisement was an accurate statement of fact, fully supported by data from the study referenced. Measurement of such a parameter was a normal integral part of assessment of glaucoma treatment over a three year period.

Allergan did not believe that the advertisement could be considered to be inconsistent with the SPC and was therefore not in breach of the Code.

PANEL RULING

The Panel noted that the SPC for Alphagan stated that it might be used as monotherapy for the lowering of intraocular pressure in patients with open angle glaucoma or ocular hypertension who were known or thought likely to be intolerant of topical betablocker therapy and/or in whom topical betablocker therapy was contra-indicated.

The Panel noted the layout and content of the advertisement. The indication, for long term IOP control, was given first followed by three stab points. The Panel noted that glaucoma was characterised by an increase in IOP which caused changes in the optic disc and typical defects in the field of vision. The Panel noted that the preservation of visual fields was a benefit of IOP control in patients with glaucoma. The Panel considered that on balance the claim referred to the feature of controlling IOP and was not a claim for an unlicensed indication as alleged. No breach of Clause 3.2 of the Code was ruled.

Complaint received 4 November 1998

Case completed 12 January 1999

CASE AUTH/795/11/98

LEO v CROOKES HEALTHCARE

Letter about Curatoderm

Leo complained about a letter sent by a Crookes Healthcare representative to a hospital doctor which compared Crookes' product Curatoderm (tacalcitol) with Leo's product Dovonex (calcipotriol) and which referred to a published study. Crookes said that the letter had been sent to answer the doctor's specific enquiries.

The letter stated that "The mean reduction in sum score of erythema, infiltration and scaling when using calcipotriol was 5.05 compared with 4.03 for tacalcitol. However, this represents a statistical, rather than clinical difference." Leo stated that the statistically significant difference in favour of calcipotriol was in fact based upon clinical features of psoriasis. Furthermore, evaluations of global improvement made by both investigator and patient showed calcipotriol to be statistically significantly more effective than tacalcitol in both evaluations. The claim that there was no clinical difference was alleged to be misleading. The Panel noted that the study showed that there was a statistically significant difference between treatment results in favour of calcipotriol and that this was not necessarily clinically relevant. This was different to the view stated in the letter that this did not represent a clinical difference. The Panel considered that the claim in the letter was misleading and a breach of the Code was ruled.

The Panel ruled that the use of the word "alleged" with reference to the statistical superiority of calcipotriol was misleading. The study had shown a statistically significant difference in favour of calcipotriol.

The statement "... our product, Curatoderm, is so well tolerated that it can be used on the face and flexures. Conversely Dovonex, the leading calcipotriol product does not bear the same licence" was ruled to be misleading as Dovonex was licensed for the treatment of flexures.

Leo alleged that the statement "... Combined Therapy (i.e. PUVA) – something that is supported by clinical evidence" was clear promotion of combined treatment with tacalcitol and PUVA. Such combined treatment was not permitted within the tacalcitol licence. The Panel noted that Curatoderm was licensed for the treatment of psoriasis vulgaris. A section of the summary of product characteristics (SPC) referred to UV therapy stating that ultraviolet light, including sunlight, might degrade tacalcitol. When combining UV-treatment with tacalcitol topical therapy, UV-light should be given in the morning and tacalcitol at bedtime. Curatoderm therapy could thus be combined with UV treatment providing certain precautions were taken. The Panel noted that the SPC referred to UV-light in general and not UVA or UVB in particular. The Panel considered that it was misleading to refer to combined therapy with PUVA (psoralens with UVA) without referring to the precautions regarding UV-light as stated in the SPC. A breach of the Code was ruled. The Panel did not consider that the statement regarding combined therapy with PUVA constituted promotion of Curatoderm outside its marketing authorization and no breach of the Code was ruled in that regard.

In response to an allegation that the letter should have borne prescribing information, the Panel noted that the Code did not cover replies made in response to individual enquiries from members of the health professions if they related to solely to the subject matter of the enquiry, were accurate and did not mislead and were not promotional in nature. In the Panel's view the letter was not accurate, it had been ruled to be misleading and was promotional in nature. The letter could not therefore take the benefit of the exemption. The letter needed to comply with the requirements for prescribing information and a breach of the Code was ruled as it had not been included.

A breach of the Code was also ruled because the letter had used Leo's brand name, Dovonex, without its consent.

Leo Pharmaceuticals complained about a letter which had been sent by a representative of Crookes Healthcare Limited to a hospital doctor. The letter compared Curatoderm (tacalcitol), Crookes' product, with Dovonex (calcipotriol), Leo's product, referring to a published study (Veien *et al* (1997)). Leo alleged that the letter was clearly promotional in content.

Crookes pointed out that the representative and a colleague had visited the skin clinic at the outpatients department of the hospital with the intention of meeting the consultant and then detailing the product to the nursing staff. In the event, they did not meet the consultant until after speaking to the nursing staff. A senior registrar attended the session with the nursing staff unannounced and requested the comparative clinical evidence to which the letter referred. In writing his letter, the representative was endeavouring to respond to specific questions raised by the senior registrar but Crookes accepted that some of his responses were not as accurately expressed as Crookes would have wished.

1 "The mean reduction in sum score of erythema, infiltration and scaling when using calcipotriol was 5.05 compared with 4.03 for tacalcitol. However, this represents a statistical, rather than clinical difference."

COMPLAINT

Leo stated that the statistically significant difference in favour of calcipotriol was in fact based upon clinical features of psoriasis. Furthermore, evaluations of global improvement made by both investigator and patient showed calcipotriol to be statistically significantly more effective than tacalcitol in both evaluations. The claim that there was no clinical difference was misleading and in breach of Clause 7.2 of the Code.

RESPONSE

Crookes acknowledged that the sentence was in breach of Clause 7.2. The paper by Veien *et al* (1997) stated in the second paragraph of the discussion that:

"In a clinical setting, it is likely that many patients will treat once daily regardless of the instructions given. Although the difference between the treatment results of once daily use of tacalcitol and twice daily use of calcipotriol (Figs 1 and 2) represents a statistically significant difference, this is not necessarily clinically *relevant.*" [Italics added]

The letter should have referred to the clinical relevance of the observed statistical difference.

PANEL RULING

The Panel noted that the study showed there was a statistically significant difference between treatment results in favour of calcipotriol and that this was not necessarily clinically relevant. This was different to the view stated by the representative in the letter that this did not represent a clinical difference. The Panel considered that the claim in the letter was misleading as acknowledged by Crookes and a breach of Clause 7.2 of the Code was ruled.

2 "It is this selection bias in favour of calcipotriol that could undermine the alleged statistical superiority of calcipotriol."

COMPLAINT

Leo said that to state that the superiority of calcipotriol was "alleged" was misleading and in breach of Clause 7.2.

RESPONSE

Crookes acknowledged that the use of the word "alleged" was in breach of Clause 7.2.

PANEL RULING

The Panel considered that the use of the word "alleged" in relation to the statistical superiority in favour of calcipotriol was misleading as acknowledged by Crookes. The study had shown a statistically significant difference in favour of calcipotriol. A breach of Clause 7.2 was ruled.

3 "... our product, Curatoderm, is so well tolerated that it can be used on the face and flexures. Conversely Dovonex, the leading calcipotriol product does not bear the same licence."

COMPLAINT

Leo alleged that this was a further misleading comparison. The Dovonex licence did in fact allow treatment of flexures. Again Clause 7.2 had been breached.

RESPONSE

Crookes acknowledged that the product licence for Dovonex did not exclude the use of the product in flexures and that, as a consequence, the statement was in breach of Clause 7.2.

PANEL RULING

The Panel ruled a breach of Clause 7.2 as acknowledged by the company. The Dovonex product licence permitted its use on flexures.

4 "... Combined Therapy (i.e. PUVA) - something that is supported by clinical evidence."

COMPLAINT

Leo stated that this was a clear promotion of combined treatment with tacalcitol and PUVA. Such combined treatment was not permitted within the tacalcitol licence and this statement was in breach of Clause 3.2.

RESPONSE

Crookes acknowledged that the product licence for Curatoderm did not include the concomitant use of the product and PUVA although advice was given on the administration of Curatoderm to patients receiving UV treatment. One paper had been published on the use of tacalcitol and PUVA in the treatment of psoriasis vulgaris and it was to this that the letter referred.

PANEL RULING

The Panel noted that Curatoderm was licensed for the treatment of psoriasis vulgaris. A section of the summary of product characteristics (SPC) referred to UV therapy stating that ultraviolet light, including sunlight, might degrade tacalcitol. When combining UV-treatment with tacalcitol topical therapy, UV-light should be given in the morning and tacalcitol at bedtime. Curatoderm therapy could thus be combined with UV treatment providing certain precautions were taken. The Panel noted that the SPC referred to UV-light in general and not UVA or UVB in particular.

The Panel considered that it was misleading to refer to combined therapy with PUVA (psoralens with UVA) without referring to the precautions regarding UV-light as stated in the SPC. A breach of Clause 7.2 was ruled.

The Panel did not consider that the statement regarding combined therapy with PUVA constituted promotion of Curatoderm outside its marketing authorization given the information about UV-light in the SPC. No breach of Clause 3.2 was ruled.

5 Use of Dovonex brand name

COMPLAINT

Leo stated that its brand name Dovonex had been used contrary to Clause 7.10.

RESPONSE

Crookes acknowledged that no direct reference by name to Dovonex should have been made in the letter.

PANEL RULING

The Panel ruled a breach of Clause 7.10 of the Code as acknowledged by Crookes.

6 Prescribing Information

COMPLAINT

Leo stated that prescribing information had not been included as required by Clause 4.1.

RESPONSE

Crookes stated that the letter enclosing the paper by Veien *et al* was sent to the doctor in response to a request for clinical evidence comparing the two products in question during a meeting at which prescribing information was supplied. No further prescribing information was supplied with the letter. It was Crookes' view that there was no requirement of the Code to enclose prescribing information with a letter to a doctor in response to specific enquiries made by that doctor.

PANEL RULING

The Panel noted that Clause 1.2 of the Code excluded from the definition of promotion replies made in response to individual enquiries from members of the health professions but only if they related to solely to the subject matter of the enquiry, were accurate and did not mislead and were not promotional in nature. Such enquiries were usually dealt with by medical information departments. The Panel thought it was unusual for representatives to respond to such requests.

In the Panel's view the letter was not accurate, it had been ruled to be misleading and was promotional in nature. The letter could not therefore take the benefit of the exemption to the definition of promotion. The letter needed to comply with the requirements for prescribing information. The Panel ruled a breach of Clause 4.1 as the letter had not included prescribing information.

Complaint received **6 November 1998**

Case completed **8 January 1999**

DIRECTOR v ASTRA

Alleged breach of undertaking

Wyeth complained that Astra had used a leavepiece for Losec (omeprazole) which bore claims similar to those ruled in breach in Case AUTH/677/2/98 and alleged that this was a failure by Astra to comply with the undertaking and assurance which it had given in that case. In view of the fact that the complaint involved a possible breach of undertaking, the matter was taken up as a complaint by the Director of the Authority as the Authority itself was responsible for ensuring compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

Wyeth supplied a copy of the leavepiece in question together with a letter from a hospital stating that it had been left there on 17 September. The Authority was able to disclose the name of the hospital to Astra but the individual did not wish to be personally identified. Astra confirmed that one of its representatives had visited the hospital on the day in question but the representative involved said that she had returned all of the leavepieces in question to head office and denied leaving any at the hospital on that day. In the Panel's view this was a case where the company needed to know the name of the individual involved so that the matter could be properly investigated. The Panel was concerned about the serious nature of the allegation that an undertaking had been breached but there was no way of resolving the conflict of evidence. In the circumstances the Panel ruled that there had been no breach of the Code.

COMPLAINT

Wyeth complained that Astra Pharmaceuticals Ltd had used a leavepiece for Losec (omeprazole) which bore claims similar to those ruled in breach in Case AUTH/677/2/98 and alleged that this was a failure on the part of Astra to comply with the undertaking and assurance which it had given in that case. Wyeth supplied a copy of the leavepiece (ref LOS MLR 2334) together with a letter from a hospital stating that it had been left there on 17 September.

Specifically, Wyeth alleged that:

1 The page 2 quotation ("Not only can Losec (omeprazole) provide greater acid suppression than lansoprazole") was in essence identical to a header previously ruled in breach.

2 The page 3 quotation ("Which in turn can increase healing") was in disregard of the Panel's advice that the study did not accurately reflect the summary of product characteristics for Losec.

3 The page 4 quotation ("...with lansoprazole, by contrast, no clinical benefit is gained by increasing the dose in reflux oesophagitis or duodenal ulcer") was essentially identical to the ruling relating to the Avner reference.

4 The page 5 depiction of the Jaspersen abstract, together with the associated quotation ("So, it comes as no surprise that in a highly acid sensitive condition, Losec can keep more patients healed than lansoprazole and also than pantoprazole") was essentially similar to the context of a page previously ruled in breach.

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

The Authority was given permission to advise Astra of the name of the hospital but not the name of the individual involved. Attention was drawn to the requirements of Clauses 21 and 2 of the Code.

RESPONSE

Astra stated that it could confirm that the detail aid and all hospital materials ceased from being used exactly as would be expected. The correspondence relating to this was provided. Astra drew attention to a memorandum of 1 September 1998 where all the representatives were instructed to use only the data sheet and clinical papers until they received the new materials. Astra had randomly checked this and the instruction had been carried out.

Astra stated that within the company it was a contractual obligation that field force staff complied with the Code. Failure to do so resulted in a disciplinary offence and under certain circumstances dismissal from the company. Astra adhered to this rule tightly.

Astra confirmed that the representative called on the hospital on the date mentioned. The representative had been questioned precisely on exactly what she did, who she called on, what she left and her understanding of the memoranda of the 20 August and 1 September 1998. The response was provided. The representative had returned all hospital leavepieces to head office via registered mail. No leavepieces had been left at the hospital on 17 September. The representative was experienced and had passed the ABPI examination.

Normally, under these circumstances, Astra's managing director would speak to the complainant personally and then speak to the representative about their interaction with this particular individual, and take appropriate action, disciplinary if necessary. This could not fully proceed without some additional information. If the Authority could gain agreement from the healthcare professional concerned, hopefully the case could be resolved. Astra's managing director was keen to do so for obvious reasons.

Astra did not consider it had failed to comply with the undertaking. On the contrary, withdrawal of all hospital material was not only fulfilling the letter of the Code but also the spirit of the Code.

With regard to the individual representative concerned, there were conflicting stories which needed resolving. The representative would be disciplined if she had used withdrawn material.

Disciplinary action in Astra was recorded on the individual's personnel record and affected their position in the company with regard to promotion and salary reviews. Therefore, it would be inappropriate to conduct a hearing without knowing the complainant's name, or without allowing the representative to defend herself.

Astra's managing director had been to see the managing director of Wyeth to discuss this issue. Astra felt strongly that if it gave an undertaking it delivered on this commitment. It was a matter of professionalism and integrity. The managing directors of Astra and Wyeth had agreed that if the issue arose again direct contact between the two would be made so that immediate action could be taken.

The response from Astra together with details of all enclosures were sent to the individual in the hospital for comment.

FURTHER COMMENTS FROM THE HOSPITAL

The individual involved stated that a detail aid outlining the Jaspersen study (amongst other things) was left at the hospital on 17 September.

The individual agreed with Astra that "it is very unfortunate that the complainant is unwilling to be named." The individual could also see that Astra would find it difficult to proceed against the representative without a name as the representative would be unable to fully defend themselves.

The individual stated that there was no intention to cause harm to an individual's career by raising the complaint. The individual stated that the aim had been to merely attempt to speak out against a company which, in their personal opinion, had repeatedly marketed within the hospital against the hospital's guidelines on the use of proton pump inhibitors. This type of marketing was to be expected, and no doubt was not unique to Astra. However the individual took very strong exception when a company misrepresented data, and continued to use this data in a fashion it had been advised against by the Authority.

The individual apologised if their unwillingness to be named had wasted the Authority's time. The individual found it frustrating that an individual could not remain anonymous when making a complaint, and there was no way that the complaint could be verified or denied by an independent third party. However the individual was reassured by Astra's comment that if such an event occurred again the managing directors of the two companies would liaise directly to take immediate action.

PANEL RULING

The Panel noted that there had been further correspondence with the hospital in question but that the individual involved did not wish to be personally identified. The Panel noted the individual's comments about remaining anonymous. In the Panel's view this was a case where the company needed to know the name of the individual so that the matter could be properly investigated.

The Panel was concerned about the serious allegation that one of Astra's representatives had breached the undertaking by leaving material at the hospital on 17 September. The individual at the hospital asserted that this was so and Astra accepted that its representative had visited the hospital on that date. The representative contended that she had not left the leavepiece on that day and there was no way of resolving the conflict of evidence. In the circumstances the Panel ruled that there had been no breach of the Code.

The Panel was concerned, however, by the lack of information which Astra had given to its representatives in relation to the rulings in Case AUTH/677/2/98. From the papers provided to the Panel, it appeared that representatives had not been told that the detail aid was in breach of the Code. A memorandum to representatives dated 20 August stated that a new detail aid was in the course of preparation and that copies of the current detail aid should be returned by the end of August. A further memorandum dated 1 September informed representatives that the new detail aid would be presented to them on 10 September. No reference was made to the rulings under the Code. The Panel considered that the position should have been made clear to representatives so that they could have understood why the detail aid had to be withdrawn. In the Panel's view the situation was such that it would have been possible for representatives to have returned the detail aid as requested but have continued to make verbally the claims that had been ruled in breach of the Code. The Panel asked that its views be made known to Astra.

Complaint received **6 November 1998**

Case completed **21 January 1999**

CASE AUTH/800/11/98

ZENECA PHARMA v GLAXO WELLCOME

Naramig journal advertisements

Zeneca Pharma complained about three advertisements for Naramig (naratriptan) issued by Glaxo Wellcome which had appeared in Pulse. On each of the advertisements was a photograph of a smiling woman with the words "It's Brilliant" underneath. Zeneca's view was that this could only refer to the product and alleged that it was an exaggerated claim implying some special quality for the product which could not be substantiated. The Panel considered that the claim "It's Brilliant" would be read as meaning that the product was excellent or superb rather than be attributed specifically to what patients might think of Naramig, as submitted by Glaxo Wellcome. The Panel noted the data provided by Glaxo Wellcome but considered that it was not sufficient to justify the use of the very strong claim that the product was brilliant. The Panel considered that the claim "It's Brilliant" was exaggerated and a breach of the Code was ruled.

The Panel ruled a breach of the Code because more than three pages in the issue of the journal bore advertising for Naramig. The Panel noted that there had been two abbreviated advertisements on separate pages and a double page advertisement.

Zeneca Pharma complained about three journal advertisements for Naramig (naratriptan) issued by Glaxo Wellcome UK Limited which had appeared in Pulse, 7 November 1998. The advertisements in question were an abbreviated advertisement on page 1 of the journal a different abbreviated advertisement on page 25 and a two page advertisement on pages 86 and 87.

The advertisements used similar photographs of a smiling woman's face. The phrase "It's Brilliant!" appeared underneath the photograph in quotation marks. The product name and other details were given either below or alongside the photograph.

1 "It's Brilliant!"

COMPLAINT

It was Zeneca's view that the claim "It's Brilliant!" referred to Naramig and that no other meaning could be drawn from the claim. Zeneca alleged that it was an exaggerated claim implying some special quality for the product which could not be substantiated in breach of Clause 7.8 of the Code.

RESPONSE

Glaxo Wellcome submitted that it considered that the use of the term "It's Brilliant!" accurately reflected how patients had assessed Naramig as a migraine treatment. It was a commonly used phrase in everyday language to describe something that was very good and reflected the patient perception of Naramig being highly regarded.

Glaxo Wellcome believed that Naramig was a very good acute migraine treatment and that the following information supported this statement.

a) Market research data - over 50% of patients rated Naramig as excellent

The Naramig advertisement deliberately depicted the statement "It's Brilliant!" within quotation marks as it was intended to convey what the patient thought of Naramig rather than being a scientific statement.

Analysis of over 100 questionnaires contained within Naramig sample packs found that:

51% of patients rated Naramig as excellent, with 81% of patients rating it as good or excellent, 93% of patients found that Naramig "got rid" of their migraine attack, 87% of patients would take Naramig again and 77% of patients rated Naramig as better than the treatments they had tried previously.

b) Clinical data - demonstrated that Naramig was a very good migraine treatment

Naramig was a fast acting and highly effective acute treatment for migraine. The clinical efficacy of Naramig was evaluated in eight studies in which over 4,000 migraine patients treated over 15,000 migraine attacks.

In common with other 5-HT_1 agonists, Naramig started working within an hour and was highly effective. Up to 76% of patients experienced headache relief at four hours after a single dose of Naramig 2.5mg.

Naramig also had other attributes which differentiated it from other 5-hydroxytryptamine (5-HT_1) agonists.

- Low rate of return of migraine symptoms

Naramig had a half life longer than any other available 5-HT_1 agonists and this might account for its long duration of action. The rates of return of headache with Naramig appeared lower than with other 5-HT_1 agonists.

Rates of return of migraine headache (recurrence) from different placebo-controlled studies:

Naramig 17-28%, zolmitriptan 22-37%, sumatriptan 22-44%, rizatriptan 33-47%.

In addition, unlike rizatriptan and zolmitriptan, Naramig had been shown to be associated with lower rates of return of headache than Imigran, the acknowledged gold standard.

- Excellent tolerability profile

The summary of product characteristics (SPC) for Naramig stated that the incidence of side effects reported in clinical trials was similar to placebo. Naramig was the only 5-HT_1 agonist to carry this statement on its SPC.

Data from double-blind, placebo controlled studies

demonstrated that Naramig tablets were very well tolerated with an adverse event profile similar to placebo.

Trials for sumatriptan, rizatriptan and zolmitriptan all indicated an incidence of adverse events higher than that seen with placebo.

The excellent tolerability profile of naratriptan compared to Imigran and zolmitriptan was further backed up by a meta-analysis by Goadsby PJ (1998) which showed that the therapeutic penalty rates from clinical trials (%) was: Naramig 0.1%, sumatriptan (50 mg) 7%, sumatriptan (100 mg) 17%, zolmitriptan (2.5 mg) 17%, zolmitriptan (5 mg) 29%. (Therapeutic penalty was the overall adverse event rate on the medicine minus the adverse event rate of placebo). Unfortunately, rizatriptan was not available at the time of this analysis.

In conclusion, Glaxo Wellcome believed that this data supported that Naramig was a very good migraine treatment. Consequently, the use of the phrase "It's Brilliant!" was an accurate reflection of how patients viewed Naramig and of the clinical data itself. Glaxo Wellcome did not believe that it exaggerated the quality of Naramig, but instead reflected its benefits and how patients felt after taking Naramig and experiencing relief from the burden of their migraine attack.

PANEL RULING

The Panel considered that the claim "It's Brilliant" would be read as meaning that the product was excellent or superb. In the Panel's view the claim would be read as a general statement rather than be attributed specifically to what patients might think of Naramig, as submitted by Glaxo Wellcome.

The Panel noted that the claim appeared in quotation marks. The market research data was based upon an analysis of 102 questionnaires contained in Naramig sample packs and completed and returned voluntarily by patients, rather than a randomized sample of patients receiving Naramig.

The Panel noted the data provided by Glaxo Wellcome. It considered that it was not sufficient to justify the use of the very strong claim that the product was brilliant.

The Panel considered that the claim "It's Brilliant" was exaggerated and a breach of Clause 7.8 of the Code was ruled.

2 Number of pages bearing advertising for Naramig

COMPLAINT

Zeneca also pointed out that the advertisements for Naramig had appeared on four pages of the journal. Since no issue of a journal could bear advertising for a particular product on more than three pages, Zeneca alleged a breach of Clause 6.4 of the Code.

RESPONSE

Glaxo Wellcome regretted that there was an error in Pulse, 7 November edition, and that advertisements for Naramig occurred on more than three pages. Whilst the amount of space taken up by the advertisements was less than three pages, Glaxo Wellcome acknowledged that this was a mistake on its part and apologised for this breach of the Code.

PANEL RULING

The Panel noted that, as acknowledged by Glaxo Wellcome, the issue of the journal in question bore advertising for Naramig on more than the three pages permitted by the Code. A breach of Clause 6.4 was ruled.

Complaint received **13 November 1998**

Case completed **6 January 1999**

CASE AUTH/803/11/98

MEDICINES CONTROL AGENCY v ROCHE

Advance information on Xeloda

The Medicines Control Agency (MCA) complained about a letter sent by Roche to consultant oncologists, oncology pharmacists and health authority pharmaceutical advisors informing them of the forthcoming introduction of capecitabine (Xeloda). The letter stated that it would initially be licensed for the treatment of locally advanced and metastatic breast cancer and, subsequently, for metastatic colorectal cancer. Background information was provided with the letter as was a reply paid card by means of which further items relating to Xeloda could be requested, these being i) an independent pharmacist drug review for Xeloda, ii) an independent clinical treatment algorithm for Xeloda in breast cancer, detailing patient types, protocols and treatment pathways, and iii) currently available Xeloda trial data. A follow up visit to provide further information and discuss the likely pharmacoeconomic impact could also be requested. The MCA noted that the Code stated that advance notification could be sent where it was likely that there would be significant budgetary implications for health authorities and trust hospitals etc, but it had to be directed only to those responsible for policy decisions on budgets and not to those expected to prescribe and it had to be non-promotional. The MCA considered that a mailing list of health professionals did not fall within those criteria and, in its opinion, the provision of a pharmacist drug review, trial data and clinical treatment algorithm, together with the dates of approval of the marketing authorizations, was promotional

The Panel noted that advance information about as yet unlicensed products had to be directed to those responsible for making policy decisions on budgets rather than those expected to prescribe. There might be some overlap between these two groups but the information had to go to individuals in the former capacity rather than the latter. By "policy decisions on budgets" was meant the overall financial planning of health authorities and trusts etc and not the management of individual departmental budgets. There was thus no *carte blanche* for sending the information to all relevant consultants, for example. Clearly policy makers receiving the information would wish to consult their clinicians etc about the likelihood of the product being used and this they could do. If further information or a presentation was then requested this could be provided, but strictly in a factual and non-promotional manner.

The Panel considered that the distribution of the advance information on capecitabine had been too wide. In the Panel's view it had not been directed only to those people responsible for making policy decisions on budgets. In addition the Panel noted that the letter indicated the likely cost of capecitabine but did not state the budgetary implications of the new treatment as was required. The letter stated that more extensive information on the potential impact of capecitabine from a budgetary prospective was available on return of the reply paid card. The material had failed to meet the requirements and the Panel therefore ruled a breach of the Code.

The Panel noted that the advance information had contained details of when capecitabine was expected to receive its marketing authorizations. The Panel considered that such information was essential to the forward planning of budgets and, within the context of advance notification, was not unacceptable. The Panel noted, however, that Roche had been very precise about when the marketing authorizations would be granted and considered that it would have been advisable for the material to have been less specific in this regard. The Panel noted that recipients of the advance information could request further information and that the Code allowed further information to be supplied or a presentation made. The Panel did not consider that the provision of such information *per se* was promotional. The acceptability of such information would depend on the content. The Panel noted that Roche had provided draft copies of the further information it planned to send but the Panel did not examine it as there was no allegation that the material itself was promotional, only that offering it was promotional. In any event the Panel could not rule upon material which had not yet been brought into use. The Panel considered that in the circumstances offering further information and giving expected dates of the approval of the marketing authorizations was not promotional and no breach of the Code was ruled in this regard.

The Medicines Control Agency (MCA) complained about a letter sent by Roche Products Limited advising of the forthcoming introduction of capecitabine (Xeloda). The letter stated that it would initially be licensed for the treatment of locally advanced and metastatic breast cancer and, subsequently, for metastatic colorectal cancer. Background information was provided with the letter as was a reply paid card by means of which further items relating to Xeloda could be requested, these being i) an independent pharmacist drug review for Xeloda, ii) an independent clinical treatment algorithm for Xeloda in breast cancer, detailing patient types, protocols and treatment pathways, and iii) currently available Xeloda trial data. A follow up visit to provide further information and discuss the likely pharmacoeconomic impact could also be requested.

COMPLAINT

The MCA stated that the material had recently been brought to its attention and it considered it to be in breach of Clause 3.1 of the Code. It was accordingly forwarding it for consideration by the Authority.

In an earlier letter to Roche (dated 22 October), the MCA had stated that Clause 3.1 of the Code allowed advance notification of unlicensed products where it was likely that there would be significant budgetary implications for health authorities and trust hospitals etc. However, the information should be directed only to those responsible for making policy decisions on budgets and not to those expected to prescribe, and should not be promotional.

Health professionals on a mailing list would not appear to fall within the criteria laid down by the ABPI. The MCA stated that the material was potentially in breach of The Medicines (Advertising) Regulations.

In a further letter to Roche (dated 18 November), the MCA had stated that it was of the opinion that the provision of a pharmacist drug review, trial data, and clinical treatment algorithm for Xeloda, together with the dates of approval of the marketing authorizations, was promotional and in breach of Clause 3.1 of the Code.

RESPONSE

Roche stated that the MCA's opinion seemed to be based on the contention that health professionals, ie clinicians, would not fall within the criteria applied to define those to whom advance notification of an unlicensed product might be sent with respect to budgetary considerations for that product.

In a letter to the MCA (dated 28 October) Roche had stated that considerable research was carried out and advice taken to define accurately those individuals involved in budgetary decisions. Personnel integrally involved in advising budgetary decision makers included senior clinicians. Consultant oncologists were sent information on capecitabine because Roche was informed that they made crucial contributions to budgetary decisions. Roche was willing to make this independent research available to the Authority to support its position. Paragraph ii) of the supplementary information to Clause 3.1 stated that information on new products should be directed at those responsible for policy decisions "rather than those expected to prescribe". The guidelines did not state that such a group which in addition prescribed "should not" be sent information and based on Roche's extensive research it considered that the mailing to consultant oncologists was justified and within the Code.

Roche maintained its opinion that the material under discussion was not promotional and in summary emphasised the following points:

- Expert panels (pharmacists and consultant clinicians) were consulted in order that Roche could be certain that information to be used in budgetary decisions was sent to those personnel integrally involved in those decisions.
- Expert panels were consulted because NHS purchasing procedures were constantly changing and it was difficult to assess which personnel were involved in budgetary decisions because they advised the final decision makers.
- Roche was advised that senior clinicians were integrally involved in budgetary decisions because they advised the final decision makers.
- Experts also provided guidance on the level of information required and this was taken into account, bearing in mind the provisions of paragraph iv) of the supplementary information to Clause 3.1.
- It would be impossible to make a valid budgetary decision in this context which was not based on efficacy, tolerability etc.
- The pharmacist drug review was highly technical and, given current marketing practice, could not be considered to be promotional in nature as it was a balanced review of the capecitabine data. In addition it was written by an eminent pharmacist who was Chairman of the British Oncology Pharmacist's Association.
- With regard to the provision of the timing of marketing approval, a decision on the inclusion of a new product in a pharmacy/specialist department budget could not be made, in practice, in the absence of that knowledge.
- The provision of the pharmacist drug review, trial data and clinical treatment algorithm was not part of the original letter but was available on request only. The Code stated in paragraph vii) of the supplementary information to Clause 3.1 that "if requested, further information may be supplied..." and therefore Roche believed it was within the Code as the additional materials were provided on a "request only" basis. As a result of the present dispute, these had not yet been through Roche's internal review/approval procedure but drafts were provided as requested.

In conclusion, having gone to great lengths to be in possession of the pertinent information regarding budgetary decision making and the personnel involved, Roche did not agree that it was in breach of Clause 3.1 either in terms of the content of the data provided or the personnel to whom the data were sent, or indeed of any of the subsections included in the supplementary information for that clause.

In Roche's letter to the MCA dated 28 October, referred to above, it stated that as part of its research to identify those individuals responsible for budgets in this therapeutic area it took advice from its expert medical and pharmacy advisory boards, and members of the British Oncology Pharmacy Association. In addition, as part of a pharmacoeconomic evaluation, it commissioned an independent consultancy to research precisely which particular professionals in hospitals were responsible for decisions on budgets involving the treatment of breast and colorectal cancer. This consultancy interviewed business managers, chief pharmacists, specialist pharmacists, directors of clinical oncology, directors of finance, and clinical directors. The advice from all of these sources was that whilst the ultimate responsibility for the budget lay with the unit clinical director or with the trust chief executive, their decision depended very much on advice from medical oncologists and oncology pharmacists. They therefore considered it to be essential to notify those people as early as possible as they were intrinsically involved in the budget planning process.

For these reasons Roche mailed only consultant oncologists (listed in the directory of hospitals and NHS trusts), oncology pharmacists through The British Oncology Pharmacists Association and pharmaceutical advisors from health authorities. No other health professional was mailed.

The format of the mailing was strictly informational and not promotional in nature. The letter was headed "Strictly confidential - for budgeting purposes only". A senior member of the British Oncology Pharmacy Committee who had advised Roche of what information

was required by those responsible for the budget planning process assisted with the drafting of the letter.

Roche said that the additional brief background information was purely factual, well referenced to publications at the American Association of Clinical Oncologists (ASCO) and designed to show in which particular subgroups of patients the new product would be used, and therefore what the potential impact from a budgetary perspective would be for trusts. Roche considered that it was important to include this information to assist in estimating the likely impact on the next year's budgets since clearly the new medicine would not be indicated for all patients with breast cancer.

It had been a single one-off mailing and no other additional material had been sent out. The additional information referred to in the pre-paid reply card was currently being finalised and had not yet been sent.

In summary, therefore, Roche believed that no breach of the regulations and Code had been made. Roche had tried to identify the individuals involved in the budgetary process for new medicines by seeking advice from a large number of sources. Although some of those identified might also be prescribers, they were not targeted for that reason.

Roche believed that the timing of the mailing in relation to the estimated possible marketing of Xeloda was appropriate for the budget planning period, and that this would have no impact on possible future prescribing.

PANEL RULING

The Panel noted that it could only judge the material in relation to the requirements of the Code. Clause 3.1 of the Code stated that a medicine must not be promoted prior to the grant of the marketing authorization which permitted its sale or supply. The supplementary information to Clause 3.1 stated that health authorities and trust hospitals needed to receive advance information about the introduction of new medicines which might significantly affect their level of expenditure during future years. At the time such information was required the medicines concerned would not be the subject of marketing authorizations and promotion of them would thus be in breach of the Code. Information on such medicines could, however, be provided as long as the information related to a new active substance, an active substance prepared in a new way, a significant new indication for an existing product or a product with a novel and innovative means of administration. Such information should be directed to those responsible for making policy decisions on budgets rather than those expected to prescribe. The likely cost and budgetary implications must be indicated and must be such that they would make significant differences to the likely expenditure of health authorities and trust hospitals and the like. Only factual information must be provided which should be limited to that sufficient to provide an adequate but succinct account of the product's properties. The information should not be in the style of promotional material and should not include mock-up drafts of summaries of product characteristics. If requested further information could be supplied.

The advance information supplied about Xeloda (capecitabine) consisted of a letter headed "Strictly Confidential - For use in budgeting purposes only". The letter stated that in quarter two, 1999, capecitabine would be licensed for use as a single agent in certain breast cancer patients and in quarter four of the same year receive marketing approval for use as a first line agent for the treatment of metastatic colorectal cancer. The estimated price per treatment cycle of capecitabine was given although this was not put in to the context of the cost of existing treatments. An attachment to the letter briefly detailed some of the clinical results observed with capecitabine. A reply paid card gave the opportunity to request more information. The Panel noted that the advance information had been sent to consultant oncologists, oncology pharmacists and pharmaceutical advisors from health authorities.

The Panel noted that the information had to be directed to those responsible for making policy decisions on budgets rather than those expected to prescribe. There might be some overlap between these two groups but the information had to go to individuals in the former capacity rather than the latter. By "policy decisions on budgets" was meant the overall financial planning of health authorities and trusts etc and not the management of individual departmental budgets. There was thus no *carte blanche* for sending the information to all relevant consultants, for example. Clearly policy makers receiving the information would wish to consult their clinicians etc about the likelihood of the product being used and this they could do. If further information or a presentation was then requested this could be provided, but strictly in a factual and non-promotional manner.

The Panel considered that the distribution of the advance information on capecitabine had been too wide. In the Panel's view it had not been directed only to those people responsible for making policy decisions on budgets. Many of those who had received the material would contribute to a greater or lesser degree to policy decisions but not all of them would have been responsible for making such decisions. In addition the Panel noted that the letter indicated the likely cost of capecitabine but did not state the budgetary implications of the new treatment as was required. The letter stated that more extensive information on the potential impact of capecitabine from a budgetary pospective was available on return of the reply paid card. The material failed to meet the requirements of the supplementary information. The Panel therefore ruled a breach of Clause 3.1.

With regard to the MCA's allegations in its second letter to Roche, the Panel noted that the advance information had contained details of when capecitabine was expected to receive its marketing authorizations. The Panel considered that such information was essential to the forward planning of budgets and, within the context of advance notification, was not unacceptable. The Panel noted, however, that Roche had been very precise about when the marketing authorizations would be granted and considered that it would have been advisable for the material to have been less specific in this regard.

The Panel noted that recipients of the advance information could request further information including an independent pharmacist's review, an independent treatment algorithm, trial data and a follow-up visit to discuss the likely pharmacoeconomic impact of capecitabine. The Panel noted that such information had not yet been provided to anyone. Paragraph (vii) of the

supplementary information to Clause 3.1 stated that if requested further information might be supplied or a presentation made. The Panel did not consider that the provision of such information *per se* was promotional. The acceptability of such information would depend on the content. The Panel noted that Roche had provided draft copies of the further information it planned to send but the Panel did not examine it as there was no allegation that the material itself was promotional only that offering it was promotional. In any event the Panel could not rule upon material which had not yet been brought into use.

The Panel considered that in the circumstances offering further information and giving expected dates of the approval of the marketing authorizations was not promotional. No breach of Clause 3.1 of the Code was ruled in this regard.

Complaint received **23 November 1998**

Case completed **25 January 1999**

CASE AUTH/804/11/98

DIRECTOR v ROCHE

Advertisements for prescription only medicines in The Health Issue

Roche voluntarily advised the Authority that the Christmas edition of The Health Issue contained advertisements for CellCept (mycophenolate mofetil) and NeoRecormon (epoetin beta), both of which were prescription only medicines. The publication was sold on the street to raise money for the Kidney Research Union Foundation. In accordance with guidance given to the Authority by the Code of Practice Appeal Board and published in the Code of Practice Review in August 1997, the Director decided that the matter would have to be treated as a complaint. The Code prohibited the advertising of prescription only medicines to the general public. It was not a matter which could be dealt with merely by way of warning.

The Panel noted the action taken by Roche to remedy the situation and that the Authority had been advised of the problem by Roche. Nevertheless, the circumstances demonstrated that better procedures needed to be in place at Roche in relation to the placing of advertisements for prescription only medicines and the Panel was pleased to note that Roche had such a review in hand. A breach of the Code was ruled.

Roche Products Limited voluntarily advised the Authority that advertisements for two of its prescription only medicines appeared in the Christmas edition of The Health Issue. The publication was sold on the street to raise money for the Kidney Research Union Foundation.

In accordance with guidance given to the Authority by the Code of Practice Appeal Board and published in the Code of Practice Review in August 1997, the Director decided that the matter would have to be treated as a complaint. It was not a matter which could be dealt with merely by way of warning.

COMPLAINT

The Christmas edition of The Health Issue contained advertisements for CellCept (mycophenolate mofetil) and NeoRecormon (epoetin beta), both of which were prescription only medicines. The Health Issue was intended for public sale. Clause 20.1 of the Code prohibited the advertising of prescription only medicines to the public.

RESPONSE

Roche stated that owing to a course of events not entirely within its control, two product advertisements appeared in the Christmas edition of the consumer magazine, The Health Issue. As soon as this unfortunate error was brought to Roche's attention the publishers and then the editors were informed and instructed to stop distribution of the magazine and to attempt to retrieve existing copies.

Roche explained that a publishing company produced, on behalf of the Kidney Research Foundation, a reference yearbook which was distributed to the medical profession in dialysis centres. Boehringer Mannheim historically advertised NeoRecormon in this book. In spring 1998, in the absence of a NeoRecormon product manager based at Welwyn, the business unit manager for transplantation/nephrology was approached by telephone regarding re-advertisement in the 1998 issue. Having confirmed that the book was for healthcare publication only, a commitment to placing advertisements for both CellCept and NeoRecormon was made.

The business unit manager was approached by the publishers in late summer, when the product manager was on annual leave, regarding advertising in the Kidney Research Union Foundation magazine (The Health Issue). It was assumed at this point that the publication had the same target audience as the yearbook and the advertising was agreed to. Copies of the magazine were requested but never received. Prior to despatching the advertisements, the business unit manager called the advertising manager to confirm that the publication was not for the public. The publishing company confirmed this to be the case but was, in fact, referring to the yearbook. The business unit manager arranged for the despatch of the two advertisements.

Upon receipt of the finished edition, it was immediately apparent to all concerned that The Health Issue was a

magazine for the general public. Unfortunately Roche received this copy four weeks after the publication was sent out to the printers. Copies were apparently sent to the company before this but had failed to arrive.

Action taken:

- The Authority was contacted immediately.
- The publishing company was contacted immediately which confirmed that it was unaware of the rules and regulations governing pharmaceutical company advertising.
- Roche contacted the Kidney Research Union Foundation on 16 November 1998 requesting immediate recall of all magazines. By 20 November 55,000 could be retrieved (38,000 from the distributors and 17,000 from the printers). Roche paid for reprinting the covers without the product advertisements, and covered all costs for reassembling and despatch of revised magazines.
- Internal processes had been amended such that in future verbal advertising commitments must be confirmed in writing on receipt of example journal and proof of distribution.

As could be seen it was an unfortunate course of events that led to this mistake being made but Roche was satisfied that not only did it take immediate action to help remedy a difficult situation but it was currently conducting a review of its own processes.

PANEL RULING

The Panel noted that advertisements for two prescription only medicines, Cellcept and NeoRecormon, had appeared in The Health Issue, which was a consumer publication intended for sale to the public. The Panel noted the action taken by Roche to remedy the situation and that the Authority had been advised of the problem by Roche. Nevertheless, the circumstances demonstrated that better procedures needed to be in place at Roche in relation to the placing of advertisements for prescription only medicines and the Panel was pleased to note that Roche had such a review in hand. A breach of Clause 20.1 of the Code was ruled.

Proceedings commenced **26 November 1998**

Case completed **19 January 1999**

CASE AUTH/811/12/98

DIRECTOR / PARAGRAPH 16 v SMITHKLINE BEECHAM

Seroxat promotional quizzes

During its consideration of Case AUTH/764/9/98 concerning the promotion of Seroxat (paroxetine) at an international exhibition, the Panel noted that exhibition panel 19 stated "Enter our daily quiz win a T-shirt". The Panel decided that the matter should be taken up with SmithKline Beecham under the provisions of Paragraph 16 of the Constitution and Procedure as a possible breach of the Code.

The Panel noted that the requirements of the Code applied to international exhibitions in the UK. Competitions had to be a *bona fide* test of skill. Prizes had to be relevant to the potential recipient's work and not out of proportion to the skill required. The Panel noted that the daily exhibition stand quiz with the prize of a designer T-shirt required delegates to answer five questions. The instructions stated that the "Answers can be found on the panels located on the SmithKline Beecham Exhibition Stand". Each T-shirt cost the company £3-08 which was acceptable but the Panel failed to see its relevance to the practice of medicine. As the answers were given on the stand the quiz was not a *bona fide* test of skill. A breach of the Code was ruled.

The Panel also considered two satellite meeting quizzes which had been held. The first focused on depression and had 250 clocks as prizes. Each clock cost £12-55. The second focused on social anxiety disorder and had 250 hockey shirts as prizes. Each cost £20 plus the cost of embroidery whch was £5 per shirt. Each quiz consisted of four questions and the instructions for entering stated that the answers would be given within the symposia. The Panel had a number of concerns about the quizzes. Firstly, it did not accept that a hockey shirt was relevant to the recipient's work. Secondly, prizes costing more than was allowable for a promotional aid had to be few in number. The Panel queried whether 250 prizes fell within the definition of "few". Thirdly the Panel did not consider that the quizzes were *bona fide* tests of skill. The Panel ruled that each satellite quiz was in breach of the Code.

During its consideration of Case AUTH/764/9/98 concerning the promotion of Seroxat (paroxetine) at an international exhibition, the Panel noted that exhibition panel number 19 stated "Enter our daily quiz win a T-shirt". The Panel decided that the matter should be taken up with SmithKline Beecham Pharmaceuticals under the provisions of Paragraph 16 of the Constitution and Procedure in relation to a possible breach of Clause 18.1 of the Code of Practice.

COMPLAINT

The Panel noted that the supplementary information to Clause 18.2 of the Code referred to competitions and quizzes. Competitions had to be a *bona fide* test of skill and recognise the professional standing of the recipients. The supplementary information referred to the cost of competition prizes. In addition, prizes had to be relevant

to the potential recipient's profession or employment. The Panel queried the relevance of a T-shirt.

RESPONSE

SmithKline Beecham said that there were three different quizzes conducted at the conference: one for each of the two satellite meetings and the daily quiz.

Copies of the questions used for the satellite meetings and on each of the four days of the conference were provided. In SmithKline Beecham's opinion, all the questions were *bona fide* tests of skill and recognised the professional standing of the recipients.

The prizes for the satellite quizzes were a hockey shirt and a clock and for the daily quiz a different type of T-shirt.

With respect to the satellite quizzes, only the first 250 correct entries for each quiz received a prize. Therefore, these prizes were available only to a small fraction of the delegates attending the meeting.

For the daily quiz, the T-shirts could be given to conference delegates only on completion (with correct answers) of the quiz card. Three thousand of these were available.

In both cases, prizes were available only at the exhibition stand.

The company refuted the suggestion that there had been a breach of Clause 18.1 and it believed that acceptance of a T-shirt or a clock following the correct completion of a quiz was consistent with General Medical Council advice.

The exhibition stands at conferences served a number of functions. Primarily, they provided delegates with an opportunity to learn more about company products directly from the company staff. They also provided a meeting place where delegates could talk and relax, away from the main conference sessions. As such the exhitibion stand needed to provide both the serious and responsible function of education while at the same time incorporating a small element of less serious distraction.

The quizzes with their prizes as an incentive, provided an element of fun while addressing the more serious educational element.

Most delegates at major international meetings such as the Collegium Internationale Neuro Psychopharmacologicum (CINP) had travelled considerable distance to attend and in common with many travellers they liked to take back momentoes of their attendance. SmithKline Beecham considered that, contrary to the Panel's assertion that the T-shirt was an inducement to prescribe, it was little more than a well established "delegate's trophy".

SmithKline Beecham pointed out that without lodging a specific complaint at this time, it was not alone in providing items that the Panel might query the relevance of to the potential recipient's profession or employment. (Indeed this was true of many if not all conferences, recent examples included toy cows provided by two named companies and a Rubic's cube by a third. There were a multitude of other examples too numerous to mention here.)

The company's defence of the T-shirt was based on SmithKline Beecham's perception about the nature of the relationship between the delegate at the conference and the company. The company believed that in accepting an item of clothing branded with the company's name the delegate was acknowledging a desire to be associated with SmithKline Beecham and its links with healthcare. In choosing to wear the company branded T-shirt as opposed to some other non-healthcare related T-shirt, the delegate could demonstrate their own commitment to healthcare. In this way SmithKline Beecham believed the T-shirt was relevant to the potential recipient's profession or employment.

The cost to the company of each item was £12.55 for the clock, £20.00 for the hockey shirt and £3.08 for the T-shirt.

The cost of the hockey shirt and the clock was justified on the grounds that the competition was a serious one and the prizes were few in number (250) compared with the number of delegates at the meeting and visiting the stand.

PANEL RULING

The Panel noted that the requirements of the Code applied to international exhibitions in the UK. Clause 3 of the Code included supplementary information regarding promotion at international meetings held in the UK of medicines and indications for medicines that did not have a marketing authorization in the UK although they were so authorized elsewhere.

The Panel noted the supplementary information to Clause 18.2 headed "Competitions and Quizzes". Competitions had to be a *bona fide* test of skill. Prizes of a higher value than would ordinarily be acceptable for a promotional aid were acceptable where the competition was a serious one and the prizes were few in number, relevant to the potential recipient's work and not out of proportion to the skill required in the competition. The maximum acceptable cost to the donor of a prize in a promotional competition was £100 excluding VAT.

The Panel examined the details given to delegates about the quizzes. The daily exhibition stand quiz with the prize of a designer T-shirt required delegates to answer five questions. The instructions about the daily quiz stated that "Answers can be found on the panels located on the SmithKline Beecham Exhibition Stand".

The Panel noted that each designer T-shirt cost the company £3.08. The cost was in line with the requirements in Clause 18.2 of the Code for promotional aids. The Panel however failed to see the relevance of a T-shirt to the practice of medicine. The prize did not meet the requirements of the Code in this regard. The Panel considered that as the answers were all given on the exhibition panels, the quiz was not a *bona fide* test of skill as referred to in the supplementary information to Clause 18.2 of the Code. Clause 18.2 of the Code gave exemptions to Clause 18.1 of the Code. It was not possible to breach Clause 18.2. The Panel therefore ruled a breach of Clause 18.1 of the Code.

The Panel then noted the arrangements for the two satellite meeting quizzes. The first satellite meeting quiz focused on depression and had 250 clocks as prizes. Each clock cost £12.55. The second satellite meeting focused on

social anxiety disorder and had 250 hockey shirts as prizes. Each cost £20.00. The Panel noted that the cost of the hockey shirt at £20.00 did not include the cost of the embroidery which was £5.00 per shirt. Each satellite quiz consisted of 4 questions and the instructions for entering the quizzes stated that the answers would be given within the symposia.

The Panel had a number of concerns about the quizzes. Firstly, it did not accept that a hockey shirt was relevant to the recipient's work. Secondly, the supplementary information referred to the prizes as being few in number. The Panel queried whether 250 prizes fell within the definition of "few". Thirdly the Panel did not consider that the quizzes were *bona fide* tests of skill. The Panel decided that each satellite quiz was in breach of Clause 18.1 and ruled accordingly.

The Panel noted the comments made by SmithKline Beecham about other prizes and quizzes at the meeting. Companies had been reminded of the requirements at international meetings held in the UK in the August 1996 issue of the Review. SmithKline Beecham could of course submit complaints about quizzes etc run by other companies.

Proceedings commenced **13 November 1998**

Case completed **21 January 1999**

CODE OF PRACTICE REVIEW - FEBRUARY 1999

Cases in which a breach of the Code was ruled are indexed in **bold type.**

700/4/98	**General Practitioner v Astra**	**Losec bonus scheme**	**Breach Clause 9.1**	**Appeal by complainant**	**Page 3**
715/5/98 & 716/5/98	**Parke Davis v Bristol-Myers Squibb and Sankyo Pharma**	**Promotion of Lipostat**	**Breaches Clauses 4.6 and 7.2**	**Appeal by respondents**	**Page 9**
728/6/98	**Glaxo Wellcome v Astra**	**Oxis Turbohaler 12 dosage card**	**Breach Clause 7.2**	**Appeal by respondent**	**Page 17**
744/7/98	**Glaxo Wellcome v Zeneca Pharma**	**Accolate journal advertisement**	**Breach Clause 7.2**	**Appeal by respondent**	**Page 21**
745/7/98	**Astra v Wyeth**	**Promotion of Zoton**	**Breach Clause 2 Four breaches Clause 7.2**	**Appeal by respondent**	**Page 24**
748/7/98	**The Liposome Company v NeXstar**	**Promotion of AmBisome and DaunoXome**	**Breaches Clauses 7.2 and 10.1 Two breaches Clause 3.2**	**No appeal**	**Page 30**
750/8/98	**Consultant Chest Physician v Glaxo Wellcome**	**Promotion of Flixotide**	**Two breaches Clause 7.2**	**Appeal by complainant**	**Page 33**
752/8/98 & 753/8/98	**Bristol-Myers Squibb and Sanofi Winthrop v Astra and Takeda**	**Promotion of Amias**	**Breaches Clauses 3.2, 7.6 and 7.8 Two breaches Clause 7.2**	**No appeal**	**Page 39**
754/8/98	**Director v Hoechst Marion Roussel**	**Nurse facilitated audit**	**Breach Clause 18.1**	**Appeal by respondent**	**Page 46**
755/8/98	**Consultant Microbiologist v The Liposome Company**	**Promotion of Abelcet**	**Breach Clause 15.9**	**No appeal**	**Page 52**
757/8/98	**Consultant Chest Physician v Glaxo Wellcome**	**"Dear Doctor" letter**	**Breach Clause 9.9**	**No appeal**	**Page 54**
759/8/98	**Glaxo Wellcome v Merck Sharp & Dohme**	**Maxalt mailing**	**Three breaches Clause 7.2**	**Appeal by respondent**	**Page 56**
762/9/98	**Shire v Zeneca Pharma**	**Zoladex journal advertisement**	**Breach Clause 7.2**	**Appeal by respondent**	**Page 61**
764/9/98	**Lilly v SmithKline Beecham**	**Seroxat exhibition stand**	**Breach Clause 3.2**	**No appeal**	**Page 66**
765/9/98	Prescribing Unit Manager v Schering-Plough	Detrunorm journal advertisement	No breach	No appeal	Page 68
766/9/98	**Pharmacia & Upjohn v Schering-Plough**	**Promotion of Detrunorm**	**Breaches Clauses 7.2 and 7.8**	**No appeal**	**Page 69**
767/9/98	**General Practitioner v Schwarz Pharma**	**Viridal Duo "Dear Doctor" letter**	**Breach Clause 4.1**	**No appeal**	**Page 71**
768/9/98	**Pharmacia & Upjohn v Allergan**	**Patient poster**	**Breaches Clauses 4.1 and 20.1**	**No appeal**	**Page 72**

769/10/98	Pasteur Mérieux MSD v SmithKline Beecham	Promotion of Typherix	No breach	No appeal	Page 74
770/10/98	Hospital Pharmacist v Lundbeck	Cipramil mailing	No breach	No appeal	Page 75
771/10/98	General Practitioner v Pfizer	Diflucan journal advertisement	No breach	No appeal	Page 76
772/10/98 & 773/10/98	**Director v Eisai and Pfizer**	**Breach of undertaking**	**Breaches Clauses 2 and 21 Report to Appeal Board**	**No appeal**	**Page 78**
774/10/98	**SmithKline Beecham v Bayer**	**Ciproxin "Dear Doctor" letter**	**Breach Clause 7.2**	**No appeal**	**Page 80**
775/10/98	Consultant Paediatrician/ Endocrinologist v Ferring	Information requested by patient's mother	No breach	No appeal	Page 82
776/10/98 & 777/10/98	**Consultant Physician v Bristol-Myers Squibb and Sankyo Pharma**	**Lipostat "Dear Doctor" letter**	**Breaches Clauses 7.2 and 8.1**	**No appeal**	**Page 85**
781/10/98	General Practitioner v Astra	Plendil journal advertisement	No breach	No appeal	Page 88
782/10/98	**Doctor v Pfizer**	**Meeting on former Royal Yacht**	**Breach Clause 19.1**	**No appeal**	**Page 91**
784/10/98	**Shire v Procter & Gamble**	**Cacit D3 journal advertisement**	**Two breaches Clause 7.2**	**No appeal**	**Page 93**
792/11/98	General Practitioner v Servier	Natrilix SR leaflet	No breach	No appeal	Page 97
793/11/98	Alcon v Allergan	Alphagan journal advertisement	No breach	No appeal	Page 98
795/11/98	**Leo v Crookes Healthcare**	**Letter about Curatoderm**	**Breaches Clauses 4.1 and 7.10 Four breaches Clause 7.2**	**No appeal**	**Page 99**
797/11/98	Director v Astra	Alleged breach of undertaking	No breach	No appeal	Page 102
800/11/98	**Zeneca Pharma v Glaxo Wellcome**	**Naramig journal advertisements**	**Breaches Clauses 6.4 and 7.8**	**No appeal**	**Page 104**
803/11/98	**Medicines Control Agency v Roche**	**Advance information on Xeloda**	**Breach Clause 3.1**	**No appeal**	**Page 106**
804/11/98	**Director v Roche**	**Advertisements for prescription only medicines in The Health Issue**	**Breach Clause 20.1**	**No appeal**	**Page 109**
811/12/98	**Director/Paragraph 16 v SmithKline Beecham**	**Seroxat promotional quizzes**	**Two breaches Clause 18.1**	**No appeal**	**Page 110**

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, more than fifty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings including payment of travelling and accommodation expenses in connection therewith
- the provision of information to the general public either directly or indirectly
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Philip Cox 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 0171-930 9677 facsimile 0171-930 4554).