PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

# CODE OF PRACTICE REVIEW

NUMBER 13

AUGUST 1996

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.

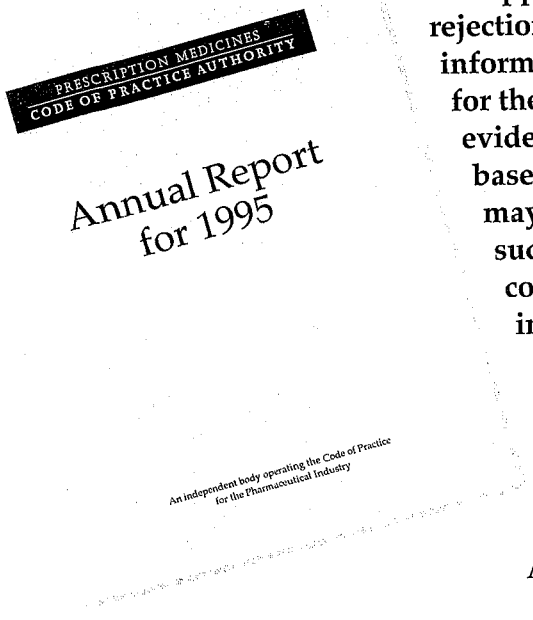
## Fewer complaints in 1995 than in 1994

**The Annual Report of the Prescription Medicines Code of Practice Authority for 1995 shows that there were 104 complaints in 1995 as compared with 145 in 1994. In the years immediately prior to 1994, there had been around 80 to 100 complaints each year and 1994 was thus exceptional in this regard.**

**By the end of July, 66 complaints had so far been received in 1996 and it looks as if the number of complaints received during the year will turn out to be something in the region of 100.**

**As in previous years, the majority of complaints (62%) received in 1995 came from health professionals. Intercompany complaints represented only 25% of the total number of complaints in 1995, though intercompany complaints tend to be of greater complexity than those from health professionals.**

**Of the 177 rulings made by the Code of Practice Panel in 1995, 147 (83%) were accepted by the complainants and respondents involved. 23 rulings (13%) were unsuccessfully appealed and 7 rulings (4%) were successfully appealed. The procedures were changed as from the beginning of 1996 to give the complainant who appeals against the rejection of a complaint more information as to the reasons for the decision and the evidence upon which it was based. As a result of this, it may be that the number of successful appeals from complainants will increase in 1996.**




**Copies of the Authority's Annual Report for 1995 are available free of charge from the Authority.**

### Exhibitions

The supplementary information to Clause 3 of the Code of Practice sets out the position as regards the promotion at international meetings held in the United Kingdom of medicines, or indications for medicines, which do not have a marketing authorization in the UK, although they are so authorized elsewhere.

Companies are reminded that at international exhibitions in the UK, the requirements of the Code apply with the exception noted above. Some companies seem to be under the impression that international exhibitions held in the UK are a kind of "no go" area where the Code does not apply. This is not the case.

Companies are reminded that gifts, hospitality and competitions associated with any meeting held in the UK must comply with the Code. It appears that some activities at such events are not in accordance with the relevant requirements of the Code.

### No more than three pages

A problem that can arise is the question of who checks that advertising for a particular product does not appear on more than three pages in a particular issue of a journal. This is a requirement of Clause 6.4 of the Code. Individual advertisements will be certified in accordance with Clause 14 but those certifying will not necessarily know what use is to be made of the advertisements concerned.

A recent instance where more than three pages in a journal bore advertising for a particular product elicited the response that this was the fault of the print buyers. Clearly companies need to incorporate into their operating procedures some means by which it will be checked that no more than three pages in any one journal will carry advertising for a particular product.

### Need an audit?

Paragraphs 10.4 and 11.2 of the Constitution and Procedure respectively allow either the Code of Practice Appeal Board or the ABPI Board of Management to require an audit of a company's procedures in relation to the Code to be carried out by the Authority. An audit of the company involved has, on occasion, been required by the ABPI Board prior to making a decision on a matter reported to it by the Appeal Board. An audit consists of an examination of a company's procedures for complying with the Code, including certification and such matters as the approval of representatives expenses, by means of an examination of relevant documents and the questioning of responsible executives.

From time to time the Authority has been asked voluntarily by a company to carry out an audit so that the chief executive could satisfy himself that his procedures were acceptable.

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

### Size of the non-proprietary name

Clause 4.2 of the Code, in respect of full advertisements, and Clause 5.4, in relation to abbreviated advertisements, say that the non-proprietary name of the medicine or the list of active ingredients, using approved names where such exist, 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 occupies a total area no less than that taken by the brand name.

Many advertisements currently appearing in journals provide the non-proprietary name in a size well under 10 point bold, which is the smallest size allowed, and companies are requested to check their advertisements to ensure that they comply with the requirements of the Code in this respect.

It is intended to start taking this matter up with the relevant companies later in the year.

### Prescribing information

Some prescribing information leaves a lot to be desired with regard to legibility.

The supplementary information to Clause 4.1 of the Code gives considerable guidance on the attainment of legibility of prescribing information. It has to be said that there has been an improvement in recent years but many advertisements still do not come up to standard. Particularly a problem are advertisements where the prescribing information is printed in a light colour against a dark background. Such advertisements tend to be very variable depending on the printing process and the type of paper on which the advertisement is printed and can be difficult to read. Companies are asked to check their advertisements in this regard and correct where necessary.

### 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:

Emer Flynn on
0171-930 9677 extn 1443.

Direct lines can be used for the members of the Authority.

David Massam 0171-747 1405
Heather Simmonds 0171-839 1058
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.

## 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 procedure 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:

Wednesday, 23 October 1996
Tuesday, 26 November 1996
Thursday, 5 December 1996

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 Emer Flynn at the PMCPA for details (0171-930 9677 extn 1443)*

CASE AUTH/387/1/96

# GENERAL PRACTITIONER v CIBA

## Promotion of Foradil and conduct of representatives

**A general practitioner complained about the promotion of Foradil by Ciba's staff at an exhibition and about their conduct.**

**An allegation that a claim that Ciba's dry powder device performed better than the Accuhaler, in terms of lung deposition, had not been substantiated by the company was upheld as Ciba had declined to provide the substantiating information, only allowing the complainant to see it but not providing him with a copy or allowing him to take a copy.**

**In relation to an allegation that Foradil had been promoted for use as relief medication, contrary to the terms of its product licence, the Panel considered that in view of the conflict of evidence, it was unable to determine whether such a claim had been made and it was accordingly ruled that there had been no breach of the Code.**

**An allegation that Ciba had failed to supply the structural formula of fenoterol, a product which it did not supply, was not upheld. The Panel considered that it was not a requirement of the Code to supply the structural formula of a competitor product for the purposes of comparison when the issue was raised by the enquirer rather than the company concerned. Ciba had provided the structural formula of its own product. There was no evidence to support an allegation that Foradil was being marketed as having the safety of salmeterol.**

**In relation to allegations about the level of knowledge and the conduct of Ciba staff, the Panel did not consider that there was any evidence upon which it could base a ruling that there had been a breach of the Code in that regard. Clearly meetings between the parties had not gone well but this was not to say that the Code had been breached.**

A general practitioner complained in a letter dated 24 January about the behaviour of three representatives of Ciba-Geigy seen by him at the company stand at the British Thoracic Society (BTS) meeting in London in December 1995. The parties were discussing Foradil (eformoterol), Ciba-Geigy's new asthma product.

The comments of the company were duly received in a letter dated 5 February and subsequently a second letter (dated 10 February) was received from the complainant following a visit to him by Ciba's marketing director. The matter was considered by the Panel and it was decided that Ciba's response should be sent to the complainant for comment and that the complainant's second letter (dated 10 February) should be sent to Ciba for comment. It was thought appropriate to take this course of action as it had on occasion been found helpful in cases where it was difficult to be certain as to what had been said and done by the parties involved. The complainant had agreed to his second letter being sent on and Ciba had also so agreed, except that it was not willing to have certain of the appendices to its response made available to the complainant.

The complainant wrote a third letter (dated 16 February) in which he commented on Ciba's response. Ciba sent a second letter (dated 21 February) in which it commented on the complainant's letter of 10 February concerning a visit to him by two of Ciba's staff.

There were three specific complaints (points 1, 2 and 3), together with a general complaint (point 4). These were considered as follows:

### 1 Lung deposition

#### COMPLAINT

The complainant said that on Monday, 11 December, he had spoken to a female representative at the Ciba-Geigy stand. She had discussed Ciba-Geigy's dry powder delivery device and had asked him for his views on it. The complainant had said that it looked fiddly and old fashioned. He had stated that we were now two generations forward with the Diskhaler and then the Accuhaler. The reply was that the company had papers to prove that it performed better than an Accuhaler in terms of lung deposition. The complainant had been amazed and had asked to see the papers. Her reply was that she did not have the papers with her. The complainant had asked her to bring the papers with her on Wednesday, 13 December, as he felt that that offered her a reasonable time to produce them. She had taken his name and agreed to this.

The complainant visited the stand on 13 December and the representative said that she "had not been able to get the papers" and that they were "data on file". The complainant had stated that he did not mind that they had not been subject to peer review and still wanted to see the data. It was an amazing claim for such a peculiar looking fiddly device. He had asked her to post the data to him and left his address. The data had not been forthcoming and he did not believe that it had ever existed.

#### SECOND LETTER FROM COMPLAINANT (DATED 10 FEBRUARY)

The complainant said that he had been visited by the marketing director of Ciba-Geigy who had been accompanied by someone else. The marketing director had stated that the data on deposition was so commercially sensitive that he was the one who had blocked its transmission to him. The marketing director said that he would show it to the complainant but it could not be taken out of the room or kept or copied. He said that he was obliged only to show the data and not to provide a copy or allow the complainant to copy it.

The "data" comprised a sheaf of papers which were said to be standard papers from the US on standards and methodology for testing inspired drugs *in vitro*. There were also a couple of pages of A4 which were headed with Ciba letter heading. These pages did not show any tables of figures. There were two bar charts. The

complainant was told that the first bar chart was a comparison of twin impinger studies, comparing Ciba's device, the Diskhaler, the Accuhaler and the Turbohaler. The second chart, the complainant was told, was from a multi-stage impinger comparing the same four devices. The complainant could not understand the commercial sensitivity of this data as there were no supporting figures or anything concerning methodology. The complainant had asked what pressure drop across the devices was necessary to develop flow rates of 60 litres per minute, which was apparently one of the standards. Neither the marketing director nor his colleague had any ideas on this and certainly did not offer to obtain the information as the whole thing was "commercially sensitive". The complainant had discussed the pressure drop of a competitor device and there was a disagreement about the resistance of the competitor device.

There were many problems with this "data" as a follow up to the representative's promise. Initially she had said that they had papers to substantiate the claim. Two days later she said it was data on file. These were totally different things. The information the complainant was shown was certainly not a paper and in fact he did not believe that there was sufficient information given to him for him to classify it as data on file. The complainant did, however, have a much bigger problem in accepting this. When the representative told him of these "papers", she had said that the methodology was the use of radio isotopes showing actual lung deposition with two detectors at right angles which sounded a pretty impressive methodology. This, however, bore no relation whatsoever to the two sheets of A4 shown to him by the marketing director which were claimed to show results of *in vitro* tests on a twin and then on a multistage impinger. The complainant did not challenge him on this as it would have been calling him a liar to his face. The marketing director continually told the complainant that his staff told a totally different story to that outlined in the complaint - which in fact accused the complainant of being a liar or of not knowing what he said or heard.

## CIBA'S RESPONSE TO COMPLAINT (DATED 5 FEBRUARY)

Ciba said that the female representative referred to by the complainant was in fact Ciba's group product manager for asthma, not a medical representative. Ciba understood that she knew the complainant and was known to him from her job with a previous employer. Had such an interview taken place with one of Ciba's representatives, no such information as was claimed could have been provided since this aspect of comparative performance of different dry powder devices did not form part of the brief or promotion. The representative would therefore have had to write to Ciba's medical department for a reply to the enquiry.

The product manager viewed the conversation as one between a product specialist (albeit a marketing one) and a doctor with an interest in the subject. It was not the usual interview between a representative and a general practitioner and her recollection of their conversation was that it was open and relaxed. The complainant's question appeared to her to be out of general interest. She certainly did not gain the impression that she was being challenged or that he was asking her to substantiate what she said because he thought she was wrong, or could not do so. Nor did she gain the impression that he was "amazed" at what she had said or that he did not believe her. She did recall him asking for further information but did not think that it was urgent or that he disputed what she had said, more that he would be interested in the further evidence.

The product manager denied categorically that she made reference to an *in vivo* comparison ie, by using lung deposition as a measure. If such a term had been used by her or the complainant she was certain that she would, at once, have qualified her reply. The comparisons to which she referred were made using *in vitro* methods, albeit employing techniques and equipment which were designed to represent, as far as possible, the *in vivo* situation. She was certain that this was made clear at the time and she was fully aware of the need to make this distinction.

The data referred to did exist and supported the information given. The product manager made it clear that these data were in an internal report which was still to be published, and, further, that similar work was underway externally. A copy of a medically approved synopsis of the relevant part of the report was attached to Ciba's response.

The product manager fully intended to have this synopsis made and shown to the complainant before Christmas but was distracted from her task by involvement with enquiries which arose from the BTS meeting and with pre and actual launch activities immediately before and after the Christmas/New Year break. The synopsis was in fact sent to a local representative for delivery to the complainant the day before his letter was written to the Authority. In view of the complaint, this was cancelled and arrangements made with the complainant for Ciba's marketing director and a local training manager to visit him with the data.

Ciba believed that the information supplied was up to date and correct and could be substantiated. It was acknowledged that there had been a delay in supplying the data but Ciba considered that there were mitigating extenuating circumstances. Given the intervening holiday period and the need to produce a synopsis of part of the confidential report, Ciba considered that the delay was understandable. With the benefit of hindsight, the delay could have been foreseen and the complainant informed when it became clear that a delay was likely and for this Ciba apologised.

## THIRD LETTER FROM COMPLAINANT (DATED 16 FEBRUARY) COMMENTING ON CIBA'S RESPONSE

The complainant said he remembered discussing clinical trials with the lady and asking if she had any data on a "head to head" comparison of Foradil versus Serevent. She had said that there were no papers available as clinical trials were at the time underway but no results were available. The complainant had said in a jocular way that he would have thought that the proper way when one product was being promoted against another was to do the clinical trials first rather than afterwards. This agreed with the reported events as stated by the product manager and he had no complaint about that.

This was, however, not the conversation about deposition studies about which he complained and he thought this was with a different lady. In that conversation there was no doubt whatsoever that he asked to see the papers there and then and when she said she had not got them he had asked her to bring them on the Wednesday, by which time she said they were not papers but data on file and he then asked her to forward them to him. That person could have been in no doubt that he was challenging her and did not believe her claim and was "calling her bluff" in asking to see the data. The complainant was adamant about this as he was equally adamant that the deposition that was mentioned was *in vivo* deposition studies using radioactive label material detected by two detectors at right angles. Of course if she had not told him of the methodology where would he have conjured that particular method up. This bore no resemblance whatsoever to the *in vitro* studies the company mentioned.

The complainant found it quite a coincidence that the data, even though it was not the data he had requested, was sent out the very day before his complaint and then was blocked as soon as he complained. There was a delay of approximately six weeks between his request for data and the subsequent complaint.

### CIBA'S RESPONSE (DATED 21 FEBRUARY) TO COMPLAINANT'S SECOND LETTER (DATED 10 FEBRUARY)

Ciba said that its marketing director visited the complainant with the sole objective of sharing the information promised at the BTS meeting. It was not his intention to discuss the complaint. The complainant raised issues within the complaint for discussion at the meeting.

There were two points in the complainant's letter that Ciba would like to address. First, Ciba's representative at the BTS had no knowledge of the use of radioisotopes using actual lung deposition with two detectors at right angles and therefore could not have had a conversation about such a device at the BTS meeting. To Ciba's knowledge no such methodology existed. She did recall having a conversation with him about various techniques in terms of methodology, but in a general sense and not in relation to Foradil. Additionally, she specifically recalled talking about studies (one ongoing, one completed), not papers, during their discussion about respiratory fraction. Ciba tried to place urgency and seriousness to the follow up to the complainant to supply him the data on file. At the meeting, the complainant indicated that data shared with him was acceptable. Ciba was obviously disappointed with his reaction but submitted that it had met its obligation to share the data on file to support its claims made by the representatives at the BTS meeting.

### RULING

As a general point which applied to the whole of the complaint, the Panel observed that it was difficult in such cases to know exactly what had transpired between the parties. Accounts differed. A judgement had to be made on the evidence which was available, bearing in mind that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint.

The Panel observed that Clauses 7.3 and 7.4 relating to the substantiation of claims applied to claims made by members of a company's staff, whether they were representatives or otherwise. Any claims made orally needed to be substantiated upon request in the usual way. It was up to a company to see that its staff were appropriately briefed and trained so that they would take care in their conversations to ensure that any claims were valid and substantiable. It was immaterial whether the claims were made on the initiative of the representative or during the course of a conversation.

In the present case, the Panel considered that a claim had been made to the effect that Ciba's dry powder device performed better than the Accuhaler in terms of lung deposition. The Panel considered that the company had failed to comply with the requirements of Clause 7.4 of the Code that "Substantiation for any information, claim or comparison must be provided without delay at the request of members of the health professions .....". The Panel considered that such data had never been supplied to the complainant. It was not just a question of a delay in providing it. Merely showing the data without providing a copy or allowing it to be copied was not sufficient to comply with Clause 7.4. The data had to be "provided" and this meant actually provided in physical form. Even now the company was declining to allow the data to be provided to the complainant (the data were in an appendix to its response which the company had said could not be passed to the complainant). If a company was not prepared to provide substantiating data because it regarded it as being confidential, then it should not make the claim in the first place. The Panel ruled there had been a breach of Clause 7.4. In view of its ruling, the Panel did not consider the nature of the data nor address the question of whether the data were in fact adequate to support the claim.

## 2 Use as a reliever

### COMPLAINT

The complainant said that the same female representative on the Ciba-Geigy stand stated that the one advantage of Foradil was its very quick mode of action compared with Serevent. She said that it was widely used in other countries as relief medication but she did say that at this moment Ciba did not have a product licence for use in such a way. If the company did not have a product licence for certain applications, was it in fact allowed to mention it? The complainant was absolutely certain that the representative raised that "advantage" rather than him asking about the speed of action. This promotional angle was obviously widespread. The previous week the complainant had been addressing a group of trainee nurse practitioners and one of them had mentioned how exciting Foradil sounded and that a representative had told her the previous week of this quick mode of action advantage. The complainant personally felt that that promotional angle should cease forthwith until Ciba had an appropriate product licence.

### RESPONSE

Ciba said that the product manager recalled the conversation, but differently. In the process of describing

the product, she referred to the rapid onset of action, which was mentioned in the summary of product characteristics (SPC), under both posology and pharmacology. The complainant asked "What would happen if it was used as a reliever?" to which the product manager replied "We cannot recommend it for such use in the UK but, in some countries, marketing authorization allows it to be used as a reliever." She was adamant that she had made it clear to the complainant that Foradil did not have a UK product licence for use as a reliever.

Ciba was promoting the rapid onset of action of Foradil but only as a clinical feature of which doctors should be aware. It was always mentioned or featured as subsidiary to the principal use and indication as a long acting beta agonist for use in patients who required long term broncodilator therapy. This was reflected in all Ciba's promotional material and reinforced in its briefing material for representatives. This was the main differentiating factor between Foradil and salmeterol, which was well understood by GPs who had been detailed on Foradil, as confirmed by market research involving a GP survey during January 1996. Doctors did not look upon Foradil as rescue therapy and Ciba was careful to point out that, should rescue therapy be needed, a short acting beta agonist should be used, again as stated in the SPC. There was no way that any employee of the company who had been party to the many briefings and training sessions on the product would do what the complainant was claiming - they all knew how counter-productive such a claim would be. As a product licence had already been granted for the product at the time of the conversation, Ciba did not see how Clause 3.1 could apply. SPCs were available, prominently, on the stand at all times and the product was described consistently with the particulars contained therein.

### THIRD LETTER FROM COMPLAINANT (DATED 16 FEBRUARY) COMMENTING ON CIBA'S RESPONSE

The complainant categorically denied that he suggested that Foradil might be used as a reliever. The person concerned had said to him that the quick mode of action aided compliance in some cases. He asked what she meant and she had said that because they felt relief they would use it again. The complainant's reply to that was to state that by definition they were not improving compliance as a preventer by getting relief. She was the one who then mentioned the product licence for relief use in other countries. The complainant entirely agreed that she stated that the UK product licence did not cover use as a reliever and he had credited her with having said that in his original letter of complaint. The thing to which he objected was that she "muddied the waters" by stating that there was a licence for relief use in other countries. In a desperate attempt to justify her mentioning other countries' product licences, Ciba's marketing director had said that there were people at the BTS from other countries. Hence, she might have felt that he was from another country. The complainant agreed that he had a fairly pronounced northern accent, but he felt that even a person from the south of England would recognise his accent as not being foreign. She knew him anyway and hence knew that he was from this country. The complainant did not see how Ciba could say that "there is no way any employee could do what [the complainant] was claiming". The trainee nurse therapist to whom he had spoken told him the advantage of the rapid onset of action which meant it could be used as a reliever. She had told him she had been told this by a representative. Was Ciba accusing them both of being liars?

### RULING

The Panel noted that there was a conflict of evidence. Ciba said that the product manager was adamant that she made it clear to the complainant that Foradil did not have a UK product licence for use as a reliever but that had never been contested by the complainant. The complainant had agreed that she had said that. His complaint was that the product manager had raised the question of the quick mode of action and that she had said that Foradil was widely used in other countries as relief medication but that at this moment it did not have a product licence for use in this way in the UK.

The Panel considered that, on the evidence before it, it was unable to determine whether the product manager had breached the Code or not and it accordingly felt bound to rule that there had been no breach of the Code. The Panel noted that the question of whether Foradil was being promoted as a reliever would come before it shortly in another case in which a journal advertisement was involved (Case AUTH/394/2/96).

## 3 Comparison of eformoterol and fenoterol

### COMPLAINT

The complainant said that he wondered whether eformoterol (Foradil) was developed from fenoterol or was even the precursor of fenoterol. He visited the Ciba-Geigy stand again on the Monday and there were two male representatives. He asked one if there was a connection between the two and he visibly saw him panic and indicate in incongruous body language "I don't know". His colleague had the most amazingly incongruent body language as he said there was no similarity whatsoever between the two. His body language said it all. The complainant asked if the representative would show him the chemical structure of the two to compare but he did not have the structure of either. The complainant was amazed that he did not know the structure and was not able to get it at such a meeting as the BTS. He had asked him to get the information before the end of the BTS meeting. The representative did give him the structure of eformoterol but he said that he could not get that of fenoterol and so did not give the information which was necessary for him to make the comparison. The complainant had subsequently obtained the structure for fenoterol and made the comparison and the two appeared to the complainant to be remarkably similar. The way the complainant viewed it was that salbutamol and salmeterol were "paired" as were fenoterol and eformoterol. If that was the case, then should eformoterol be marketed as having the safety of salmeterol but cheaper?

### RESPONSE

Ciba said that the comments about body language were

highly subjective and unanswerable in any objective sense. Ciba therefore concentrated on the other points raised. The first of these seemed to be that its representatives were unable to meet requests for further information with regard to the comparison of fenoterol and eformoterol, they were unable to immediately produce the structural chemical formula for eformoterol and they were unable subsequently to produce the same formula for fenoterol ( a product not marketed by Ciba).

The second point was that Ciba were marketing eformoterol as having the safety of salmeterol but cheaper and should not do so on the basis that eformoterol and fenoterol were chemically similar.

In relation to the comparison between eformoterol and fenoterol, it was understandable that the first representative could not answer. Such a topic took no part in the training. His reply of "I don't know" was reasonable and credible. The second representative was actually another product manager. He denied that he said or would have said, that there was no "similarity whatsoever" between the two medicines. The essence of what he believed he had said was that "while all beta agonists have some similarities, they are all different and it is difficult and erroneous to impute clinical consequences from chemical similarities or differences". It was then the first representative, not the second as the complainant stated, who provided him with the chemical structure of eformoterol. Having been told that the representative could not get the formula of fenoterol at the meeting, which again was quite understandable in Ciba's view, the complainant did not ask the representative to send further information to him.

It was not reasonable to expect the representative to respond knowledgeably upon comparisons between medicines when these were based on purported chemical similarities. Ciba avoided such comparisons as it believed them to be potentially misleading and certainly no guide to any assessment of comparative safety or efficacy. Ciba had taken expert advice from both a clinician and a chemist within the company and they had both stated that there were no chemical or pharmacological significant similarities between fenoterol and eformoterol. Any similarities were no more than would be expected of a group of medicines with a common ancestry of isoprenaline.

Ciba was not surprised that the representative did not have the chemical structure of eformoterol product immediately to hand. It did not train its representatives to discuss chemical structures in any detail. Ciba considered such information to be of dubious relevance to the clinical performance of the medicines and that it had many pitfalls. Ciba expected its representative to be able to produce the formula reasonably quickly and this was done, as the complainant acknowledged.

Ciba did not consider that it was part of the normal duty of the representative to have available the chemical structures of other medicines, from other manufacturers, to which Ciba's might be compared. If it was relevant as part of general background such information with regard to commonly used medicines were included in Ciba's training, but this did not encompass medicines which were not widely used, such as fenoterol, and Ciba would discourage any such comparison.

Eformoterol was not marketed as having the safety of salmeterol, though the relative costs of the two medicines did form part of Ciba's brief to representatives.

### THIRD LETTER FROM COMPLAINANT (DATED 16 FEBRUARY) COMMENTING ON CIBA'S RESPONSE

The complainant said that the representative did in fact say that there was no similarity between the two. Whilst the representative might wish that he had said "the essence of what he believes he said" that was not what he did say which was the basis of the complaint. If the representative had said that "while all beta agonists have some similarities, they are all different and it is difficult and erroneous to impute clinical consequences from chemical similarities or differences", then the complainant would not even have thought of complaining.

### RULING

The Panel noted that the company had supplied the structural formula of its own product, eformoterol, reasonably promptly. The Panel did not consider that it was a requirement under the Code to supply the structural formula of a competitor product for the purposes of comparison when the point was raised by the enquirer rather than by the company concerned, though it thought most companies would do so on request. It was ruled that there was no breach of the Code in this respect.

Because of the conflict of evidence there was no basis upon which a ruling of a breach could be founded in relation to the alleged claim about safety.

## 4 General

### COMPLAINT

The complainant said that he was not impressed with the level of knowledge of any of the Ciba representatives - particularly as they were at the BTS meeting with a new product. Their greatest sin was their apparent lack of integrity. The complainant acknowledged that Ciba was new in the respiratory field but it should be capable of a better performance.

### RESPONSE

In relation to the question of the knowledge and integrity of its representatives, Ciba outlined the training of these. All the staff on the stand had passed the ABPI representatives' examination except the male product manager who was a pharmacist and who had not sat the ABPI examination because he had never been a representative. All had been trained in the area of asthma over the past 2-3 years. The representatives on the stand were very experienced hospital representatives who were regarded as possibly the most able and knowledgeable members of the general field force and who behaved with the utmost integrity. Naturally Ciba was concerned that the complainant had gained the impression that he described, but, having talked to the people involved, Ciba believed that he was mistaken in this impression.

### RULING

The Panel considered that it appeared that the personnel involved could have been better prepared for the questions they were likely to be asked at such a meeting as the one in question, given that Ciba had a new asthma product and it was inevitable that its representatives would be asked about how the new product would compare with existing products, such as in relation to the merits of various inhalers as regards lung deposition.

The Panel nonetheless did not consider that there was any evidence upon which it could base a ruling that there had been a further breach of the Code in relation to the conduct of the representatives. The various meetings between the complainant and members of Ciba's staff had not gone well but this was not to say that the conduct of the company people concerned was such as to breach the Code.

**Complaint received** 26 January 1996

**Case completed** 3 April 1996

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**CASES AUTH/394/2/96 & AUTH/407/3/96**

# GLAXO WELLCOME & GENERAL PRACTITIONER v CIBA

## Promotion of Foradil

**Glaxo Wellcome complained about a number of promotional items for Foradil issued by Ciba. A general practitioner also complained about one of the items in question.**

**An advertisement for Foradil was ruled to be in breach of the Code as it emphasised the product's speed of onset rather than its duration of action. The Panel considered that this gave the impression that Foradil could be used as a reliever in acute asthmatic attacks. This message was inconsistent with the licensed use of the product.**

**The Panel ruled that a leavepiece which mimicked the published British Thoracic Society Guidelines was misleading. Some of the wording had been changed and Foradil had been included giving the impression that the product was mentioned in the guidelines and this was not so. A general practitioner raised similar concerns about this piece.**

**A "Dear Doctor" letter was ruled to be in breach of the Code as it included a misleading price comparison of Foradil with Serevent.**

### 1 Advertisement in GP 5, January 1996

The advertisement depicted an action shot of a group of runners from the shoulders to the ground and carried the strap line "...it's quick off the mark and lasts the distance". The first part of the strap line "...its quick off the mark" was in large type immediately below the feet of the runners and the second half "...and lasts the distance" was in smaller type underneath. Three other claims were included "Complements inhaled corticosteroids", "Relieves for 12 hours" and "Begins to work in less than 3 minutes".

#### CASE AUTH/394/2/96

#### COMPLAINT

Glaxo Wellcome UK was concerned that Ciba Pharmaceuticals was promoting its product Foradil not only as a long acting bronchodilator, but also as a "reliever" medication, ie outside the product licence.

The company pointed out that more prominence was given to the first part of the strap line, ie "...it's quick off the mark" than the second part "... and lasts the distance". Being not only more prominent, but also juxtaposed with images of sprinters, this was clearly intended to promote speed of onset over and above duration of action. This conveyed to readers the impression that Foradil was rapidly effective in relieving bronchospasm, and therefore could be used as a reliever therapy. This was directly contrary to the terms of the product licence which stated that Foradil was not for relief of acute asthma symptoms.

The message was further endorsed by the claim "relieves for 12 hours" and, importantly, using the blue colour coding for Ciba's device (and supporting educational packs) which was conventionally used for reliever inhalers. Glaxo Wellcome alleged that this was not only misleading to the medical profession, but potentially confusing and hence dangerous for patients.

Since Foradil was not licensed as a reliever therapy, and since speed of onset conferred no advantage in a maintenance treatment (beyond the first dose administered), Glaxo Wellcome alleged that the strap line and artwork were misleading by implication and in breach of Clauses 3.2, 7.2 and 7.6 of the Code.

#### RESPONSE

Ciba said that the advertisement had already been the subject of correspondence with Glaxo Wellcome and, although it was confident that it did not mislead, the advertisement had already been suspended. This had been communicated to Glaxo Wellcome.

The strap lines "its quick off the mark" and "lasts the distance" were intended to be viewed in the context of the illustration. This was not a picture of a sprint race; it was clearly a photograph of long distance runners. This could been seen from the upright stance of the runners, the number of runners, and the fact that they were running on grass with muddy shoes. Ciba did not consider these to be the circumstances of a short, fast race. The temporal relationship of speed of onset followed by prolonged duration of action also had a certain logic to it. Whilst the impression of speed was undoubtedly given (and intended) so also was the context of the staying power of the long distance athlete, the strap lines and the

supporting claims. The latter were clear, few in number, unburdened by voluminous body copy and positioned in the part of the advertisement where the eye normally came to rest after scanning it, and thus the area of the advertisement where final impressions were confirmed and reinforced.

Glaxo Wellcome appeared to be inferring that the rapid onset of Foradil's action was not relevant to its clinical use and should therefore not be featured. Ciba took the opposite view. With the only other long-acting beta 2 agonist having a slow onset of action, doctors might assume that Foradil would be the same. Patients, however, would be unaware of the rapid effect of this new medication and would not be informed about it. Thus Ciba believed the responsible course of action was to ensure that doctors were made aware of this differentiating property of Foradil.

The word "relieves", in the claim "Relieves for 12 hours", was preferred to the alternatives such as "protects" or "controls". Ciba was confident that the use of the word "relieves" was well understood and positioned the product for use as a long acting bronchodilator. The use of either of the alternative words could give doctors the impression that Foradil had antiinflammatory properties and this was something Ciba was keen to avoid.

Ciba was not aware of any formal colour coding standard for long acting bronchodilators. The use of blue for the inhaler device, its package and patient information were consistent with the current practice, to use blue for bronchodilators. The blue colour of the device had been accepted, without adverse issues arising, by the Medicines Control Agency (MCA) and samples had been made available for examination by the Committee on Safety of Medicines (CSM). The colour was included as one of the registered details of the product licence.

Ciba took most seriously the charge that its promotion was potentially dangerous for patients and wished to refute it most strongly. The patient information leaflet contained instructions to take Foradil morning and evening and not in between; the patient was warned **not** to take Foradil for attacks between doses. In addition Ciba had calendar-packed the capsules to ensure that the correct doses were taken.

Ciba submitted that Foradil was being promoted entirely within the terms of its product licence. The positioning of Foradil was clearly supported by the details of its summary of product characteristics (SPC); it was fully consistent with the approved indication and the description of its pharmacology.

There was no intent to mislead. Market research of Foradil advertisements and presentations by representatives provided no evidence that doctors were looking upon Foradil as anything other than a long acting bronchodilator for use as a complement to inhaled corticosteroids.

The illustration in the advertisement together with the accompanying copy was correctly perceived by an overwhelming proportion of doctors to be consistent with the long acting nature of the drug and the correct positioning of the drug.

**RULING**

The Panel considered that the advertisement emphasised speed of onset rather than duration of action. The Panel accepted that the photograph was of long distance runners as submitted by Ciba, and not sprinters but considered that the content of the photograph, being shoulder downwards shots of athletes, made it difficult to make that distinction. There was a clear impression of speed from the photograph and this was emphasised by the large type of the first half of the strap line "...quick off the mark" which appeared immediately below it. The speed theme was reinforced by one of the claims "Begins to work in less than 3 minutes". The Panel noted from the market research that the key message to GPs related to rapid onset/speed.

Given the emphasis on the speed of action in the advertisement by the copy and the photograph, the Panel considered that it gave the impression that Foradil could be used for acute therapy. This was not in accordance with the SPC which stated that Foradil was for patients requiring long acting bronchodilators for maintenance bronchodilator therapy and a beta agonist with a short duration of action should be used in acute attack. The advertisement was therefore misleading and promoted Foradil for a use inconsistent with its SPC. The Panel ruled breaches of Clauses 3.2 and 7.2 of the Code.

The Panel took the view that the colour of the device was not relevant to the advertising of the product. The Panel also noted that the MCA had not objected to the use of blue as the colour and that it was included in the licence particulars.

## 2 Leavepiece (ref G1386 Sept 95)

One side of this laminated leavepiece featured a picture of a swimmer, product claims, and the prescribing information for Foradil. The reverse was headed "BTS Guidelines, Management of chronic asthma in adults". Underneath were six columns. The columns were headed "Step 1" and "Step 2" etc through to "Step 5" with the final column headed "Stepping down". Steps 3, 4 and 5 referred specifically to Foradil as an example of a long acting beta 2 agonist. The leavepiece used a similar layout to the official British Thoracic Society (BTS) Guidelines published in The Journal of the British Thoracic Society. In the published BTS Guidelines no specific examples were given of long acting beta agonists.

**COMPLAINT**

Glaxo Wellcome alleged that the leavepiece misrepresented the published BTS Guidelines. It clearly positioned Foradil as an alternative to increasing the dose of inhaled steroids at Step 3 of the published BTS Guidelines.

Although the published BTS Guidelines were in the process of being revised, and might in the future recommend a clear "either/or" choice at Step 3, the notes on treatment of chronic asthma in adults stated that the major role of inhaled long acting beta agonists was as a twice daily treatment in Step 4, but their use may be an alternative to increasing the dose of inhaled steroids in those having problems with this treatment. Ciba appeared to have made assumptions about what the future content

of the next guidelines would be.

Glaxo Wellcome said that the promotional material misrepresented the positioning of long acting beta 2 agonists (and Foradil specifically) within the current published BTS Guidelines and gave the impression that Foradil was recommended by name in the published BTS Guidelines.

Glaxo Wellcome had written to Ciba to request data to substantiate any claims regarding the synergistic or additive effect of Foradil with steroids but Ciba had failed to reply within the requested time frame. In addition, at a press briefing reported in Scrip, a doctor, speaking on Ciba's behalf, stated that "Efomoterol may in the future be used as an alternative to increasing the steroid dose, although there are as yet no clinical data to support such a role". Despite this Ciba were clearly promoting Foradil in this way. Breaches of Clauses 7.2 and 7.4 of the Code were alleged.

### RESPONSE

Ciba submitted that Step 3 of the published BTS Guidelines included long acting beta agonists as a therapy option. In employing the plural form, one assumed that the published BTS Guidelines were inferring that there was the potential for there being more than one long acting beta agonist available to doctors; there were in fact now two, Glaxo Wellcome's product and Foradil.

The wording in the leavepiece was quite compatible with the published BTS Guidelines. The leavepiece clearly stated that the use of long acting beta agonists (eg Foradil) in Step 3 was an option for patients who were having problems with high dose inhaled steroids. There was no attempt, in fact or intention, to claim uniqueness in this regard for Foradil. Ciba said the use of "eg" did not exclude the use of any other long acting beta 2 agonist. Indeed it failed to see how the complainant could think that it was claiming a major role in Step 3; such a conclusion was at variance with what was actually printed. The positioning of Foradil was exactly in line with that given for long acting beta agonists in each of the Steps 3-5.

In view of the nature of the leavepiece, which was after all devoted to information on Foradil, Ciba considered it was reasonable, and in keeping with accepted practice, to cite its product as an example of such a class of drug.

Ciba refuted the allegation it they had claimed a synergistic or added effect of Foradil with steroids in the sense that it improved the antiflammatory response. The indication in the SPC clearly stated that Foradil should normally be used in patients receiving regular and adequate doses of steroids and/or sodium cromoglycate. A prerequisite, therefore, for the use of Foradil was that patients should already be using corticosteroids (or sodium cromoglycate) and that the addition of Foradil to this regimen could be expected to confer an added benefit and in this sense complement existing therapy.

In relation to the criticism of the comment at the Press briefing, which was reported in Scrip, Ciba pointed out that the all important introductory phrase "In poorly controlled asthmatics on low dose inhaled steroids..." had been omitted from the section quoted. This made it clear that the doctor was referring to a specific group of patients. That was his view as an experienced clinician, who also happened to be on of the Standards Committee of the BTS; he did modify his statement by adding the comment that there was as yet no clinical data to support it. Ciba was not promoting Foradil for such patients or making the claim alleged. Nor would it, without strong evidence, wish to do other than promote Foradil as a long acting bronchodilator and avoid any inference to steroid-sparing or antiinflammatory activity.

The use of Foradil was as a therapeutic adjunct and support to the use of inhaled steroids. This was included in the indications in the SPC and therefore formed part of Ciba's product licence. Ciba did not believe therefore that it had to provide substantiation.

**AUTH/407/3/96**

### COMPLAINT

A general practitioner complained about the use of the BTS Guidelines in promotional material for Foradil. The complainant alleged that it was wrong for the text of the published BTS Guidelines to be altered in the promotional material and for the product name Foradil to have been inserted.

### RULING

The Panel noted that the reference to BTS Guidelines on the leavepiece mimicked the style of the original document, the published BTS Guidelines. Some wording had been changed. In particular the inclusion of "(eg Foradil)" and the paraphrasing of Step 3. In the Panel's view the published BTS Guidelines were generally accepted as setting out the basic principles in the treatment of chronic asthma and could therefore be considered to have considerable influence over prescribing doctors. The Panel considered that given the layout of the leavepiece, which mimicked the published BTS Guidelines, and its heading "BTS Guidelines Management of chronic asthma in adults" a doctor reading the leavepiece would assume that he was reading the published BTS Guidelines and this was not so. Consequently readers might therefore conclude that Foradil was specifically mentioned in the published BTS Guidelines which was not so. The Panel decided that the leavepiece was misleading and ruled a breach of Clause 7.2 of the Code.

## 3 "Dear Doctor" letter (ref G1261)

The "Dear Doctor" letter together with a brochure describing the Foradil patient education pack formed a launch mailing sent to hospital doctors and general practitioners.

### COMPLAINT

Glaxo Wellcome drew attention to a claim in the "Dear Doctor" letter "Foradil costs almost 20% less than the only other long acting inhaled beta 2 agonist currently available". No mention of the dosage used for the price comparison was given. The standard maintenance dose of Serevent was 50mcg twice daily, and the standard

maintenance dose of Foradil was 12-24mcg twice daily.

Since Ciba had selectively based the price comparison on the lower (12mcg) dose only, and this was not stated in way in the material, Glaxo Wellcome alleged that this was misleading in breach of Clause 7.2 of the Code.

Glaxo also alleged that Ciba had failed to reflect all the available evidence, ignoring studies which suggested that 12mcg tds or 24mcg bd might more appropriate dosage regimens and the comparable dosage regimen to Serevent 50mcg bd.

## RESPONSE

Ciba acknowledged that the Foradil SPC gave a dose range of 1 to 2 inhalation capsules twice daily. However the three available clinical studies had shown that only a minority (between 20% and 35%) of patients, those with severe asthma, required the higher dose and this was reflected in the promotion and the literature, where 12mcg was the unit of dose which was featured. The "Dear Doctor" letter and the detail aid emphasised the 12mcg, taken twice daily, as the usual maintenance dose.

As the most frequently used dosage unit of salmeterol was 50mcg, Ciba believed it to be appropriate to make the price comparison on the basis of what its clinical trials showed, and it promoted, to be the most widely used dosage unit of Foradil.

A total of four published studies had compared Foradil and salmeterol (using metered dose inhalers only). Two studies showed Foradil 12mcg and salmeterol 50mcg to have an equal bronchodilatory effect.

Two further studies (cited by Glaxo Wellcome) compared Foradil 24mcg and salmeterol 50mcg and also found an equal bronchodilatory effect. (Foradil 12mcg was not included in these studies).

These studies merely reflected the shallow dose response curves of both products. Indeed, only one of the four published Foradil dose response studies showed a significant clinical advantage of Foradil 24mcg over Foradil 12mcg. Three of the four equivalent salmeterol studies showed a small but significant clinical advantage of salmeterol 100mcg over salmeterol 50mcg. It was therefore not surprising that some studies managed to show an equivalence between high and low dosages of the different products. Nevertheless, Ciba considered that the dose unit which would prove to be the most widely used in clinical practice, and which was therefore the most appropriate for use as a basis for comparison with the most often used dose of salmeterol, was the dose of 12mcg bd.

## RULING

The Panel noted that the submission from Ciba did not include details of the costs etc used to obtain the 20% figure. It would have been helpful if this information had been provided. The Panel noted that the "Dear Doctor" letter did not give any details of the doses used as the basis for the claim that Foradil cost 20% less than Serevent. In its view, the claim was based on comparison of Foradil 12mcg twice daily with Serevent 50mcg twice daily. The Panel noted the Foradil SPC stated that "...1-2 inhalation capsules to be inhaled twice daily.." The data sheet for Serevent Diskhaler stated one 50mcg blister twice daily and in patients with more severe airways obstruction 2x50mcg of Serevent twice daily. Unlike the Serevent data sheet, the Foradil SPC made no reference to dosages for patients with more severe airways obstruction.

The Panel noted from Ciba's submission that the data also showed that 20-35% of patients required the higher dose of Foradil. In the Panel's view while this was the minority, and presumably those with severe asthma, it would more or less wipe out the claimed 20% saving with Foradil.

Given the range of the dosage of Foradil, the Panel considered that the cost comparison claim was too simplistic. No information had been given about the doses used as the basis for the comparison. The Panel considered that the claim should have reflected the costs of 20-35% of patients on the higher dose of Foradil. The Panel decided that the claim was misleading as it was not sufficiently qualified. The Panel therefore ruled a breach of Clause 7.2 of the Code.

**Complaints received**

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|---|---|
| **Case AUTH/394/2/96** | **1 February 1996** |
| **Case AUTH/407/3/96** | **5 March 1996** |
| **Cases completed** | **3 April 1996** |

CASE AUTH/398/2/96

*NO BREACH OF THE CODE*

# GLAXO WELLCOME v LILLY

## Axid advertisement

**Glaxo Wellcome alleged that an advertisement for Axid issued by Eli Lilly was unacceptable as it made a parody of both the visual and the text of current Zantac advertisements.**

**Bearing in mind Glaxo Wellcome's advertisement for Zantac, the Panel did not accept that the Axid advertisement disparaged Zantac. It did not accept that the implication about the cost of Zantac was exaggerated or misleading and the claim "An H2 antagonist that won't blow your budget" had been substantiated. No breach of the Code was ruled. This ruling was upheld by the Appeal Board on appeal from Glaxo Wellcome. The Appeal Board considered, however, that it would not be in the industry's interest for the use of parody to become widespread and could envisage such activity deteriorating into abusive exchanges between competitor companies.**

Glaxo Wellcome UK complained about a journal advertisement for Axid (ref AX385 December 1995) issued by Eli Lilly and Company Limited which appeared in Doctor 1 February 1996. The advertisement was headed with a claim "With some H2 antagonists, it's the cost that's fantastic" beneath which was a photograph of a fan blowing bank notes about.

### COMPLAINT

Glaxo Wellcome alleged that the advertisement was a flagrant example of "knocking copy" in that it disparaged Glaxo Wellcome by making a parody of both the visual and the text from current Zantac advertisements. A breach of Clause 8.1 of the Code was alleged. The current Zantac advertisement was a photograph of a fan followed by "tastic".

Glaxo Wellcome also alleged that the implication of the Axid advertisement was that the cost of Zantac was fantastic while that of Axid was not and this was misleading and exaggerated in breach of Clauses 7.2 and 7.8 of the Code.

Finally, Glaxo Wellcome drew attention to a claim, beneath the photograph, that Axid was "An H2 antagonist that won't blow your budget". The company alleged that the claim was exaggerated and could not be substantiated in breach of Clauses 7.2 and 7.3 of the Code.

### RESPONSE

Eli Lilly explained that the aim of the advertisement was to highlight the difference in cost between Zantac and Axid. It was not intended in any way to disparage Zantac. The company submitted that by saying that Axid was equally effective and equally well tolerated it was using ranitidine (Zantac) as a benchmark product.

The company submitted that the claim "With some H2 antagonists, it's the cost that's fantastic" was fully qualified in the text immediately below the headline and should be read in context and not in isolation. There were H2 antagonists available which cost significantly more than Axid. The term "fantastic" also related to the visual.

Eli Lilly submitted that the claim "An H2 antagonist that won't blow your budget" was not misleading or unsubstantiated. Given that some other products were more expensive than Axid, the claim was fully supported. Axid was 20% cheaper than Zantac and 22% cheaper than Pepcid for 30 days treatment. The claim described Axid as being "an" H2 antagonist and not "the" H2 antagonist.

### PANEL RULING

The Panel examined the advertisements for Zantac and Axid. The Axid advertisement was clearly based on the Zantac advertisement and made use of the fan and "tastic" theme which had appeared in the Zantac advertisement. The Axid advertisement featured on the difference in price between Zantac and Axid and stated that switching to Axid could save £5 per treatment course which gave 19% off the bill.

The Panel considered that the advertisement was a creative reflection of Glaxo Wellcome's advertisement for Zantac, which implied the word "fantastic" as a description of the product. The Panel did not consider that the theme in itself disparaged Zantac. It was a robust form of advertising but, in the Panel's view, not an unacceptable one and not one which amounted to disparagement. It was ruled that there had been no breach of Clause 8.1.

In other circumstances, the word "fantastic" might be regarded as exaggerated and unacceptable *per se* but it was the word Glaxo Wellcome had conveyed in relation to Zantac. The Panel considered that it was not unacceptable to describe the cost of ranitidine as fantastic given that the Zantac advertisement described Zantac as fantastic and that switching to Axid would save £5 per treatment course. Given the circumstances, the Panel did not accept that the implication that the cost of Zantac was fantastic was exaggerated or misleading and therefore ruled no breach of Clauses 7.2 and 7.8 of the Code.

The Panel considered that the claim "An H2 antagonist that won't blow your budget" was not unreasonable as using Axid would save on treatment costs compared to using Zantac and some other H2 antagonists. The claim was not that Axid would be the cheapest H2 antagonist. Generic cimetidine would no doubt be the cheapest H2 antagonist. The Panel noted from Eli Lilly's submission that the cost of 30 tablets of Axid 300 mg was £21.74, Zantac 300 mg was £27.43 and Pepcid 40 mg was £28.50. The claim had been substantiated by Eli Lilly. The Panel ruled no breach of Clauses 7.2 and 7.3 of the Code.

### APPEAL BY GLAXO WELLCOME

Glaxo Wellcome believed that the advertisement in question was a flagrant example of "knocking copy" in that it disparaged an activity of Glaxo Wellcome by

making a parody of both the visual devices and text from a current Zantac advertisment. The Panel had considered that the advertisement was a creative reflection of Glaxo Wellcome's advertisement for Zantac, whereas the company believed it was designed to disparage, that was to say it depreciated Zantac by turning the current promotional campaign against it with misleading, exaggerated and unsubstantiated claims. This unjustified "knocking copy" further depreciated Zantac by the use of the fan which, as part of an advertising campaign, was becoming synonymous to the brand's total identity as was an apple for Voltarol and a lion for Naprosyn.

The Panel had stated that in the circumstances it was acceptable to describe the cost of ranitidine as "fantastic" given that this word had been used in relation to Zantac. Glaxo Wellcome submitted that the word "fantastic" in the Zantac advertisement was substantiated by the statement that "Zantac remains the world's most prescribed anti-ulcerant" which the company believed was supported by the fact that this had placed Zantac in the Guinness Book of Records. There were many historical aspects of Zantac which could justify the description of "fantastic" ie in the colloquial sense of excellent. The company believed that to turn this round into a statement that "With some H2 antagonists [implying Zantac], it's the cost that's fantastic" was misleading and exaggerated. The company submitted that, if the claim that about £27 per month (the cost of Zantac) was a "fantastic cost" was acceptable, then it could not see how Eli Lilly could substantiate a claim that £5 less per month was not a "fantastic cost". Furthermore, claims of cost savings by switching from Zantac to Axid should take account of the fact that commonsense and audit had shown that a substantial proportion of patients who were switched would be dissatified with the change in treatment.

Glaxo Wellcome did not accept that the impression that using Axid could save on treatment costs because it was cheaper than Zantac and the suggestion that Zantac would "blow a GP's budget" were capable of substantiation. Data from prescription monitoring sources, such as IMS, indicated that while the overall national sales for gastrointestinal medicines were increasing, sales of Zantac were stable.

Finally the company said that the claim that Axid was "equally effective" and that "the big difference" was cost was misleading as it ignored other big differences, namely that Zantac had a wider range of licensed indications and a safety profile derived from far greater worldwide patient exposure.

## RESPONSE FROM ELI LILLY

Eli Lilly submitted that aim of the advertisement was to highlight the difference in cost between Zantac and Axid. It was not intended in any way to disparage Zantac. Indeed by saying equally effective and equally well tolerated it was using ranitidine as a benchmark. The advertisement had been tested to ensure that general practitioners did not consider that it breached Clause 9.3 of the Code. No doctor considered the advertisement to be misleading or confusing.

Eli Lilly did not accept that the fan was synonymous with the total brand identity as submitted by Glaxo Wellcome. Examples of an apple for Voltarol and a lion for Naprosyn were not comparable. In both of these instances one visual image was always employed as a marque of the brand. In contrast, Zantac had been portrayed using several images: a fan, an inkwell, a cent, an egg and even a fez hat.

Eli Lilly submitted that the use of the word "fantastic" was fully qualified in the text immediately below the headline and should be read in context and not isolation. The company was somewhat surprised by the choice of the Guinness Book of Records for reference to support the claim that Zantac was "fantastic". While no doubt this was a commercial fact the company was uncertain whether it was an appropriate description for a medical audience of a product which was essentially an extension of research carried out earlier by other companies and researchers. The company disputed the fact that "fantastic" was a colloquial form of excellent. It was not. It was an entirely different word with an entirely different meaning. The company did not understand the comments from Glaxo Wellcome regarding audit and switching patients as the advertisement was designed to highlight the benefit to a general practitioner who switched to Axid. The advertisement was not talking about specific patients.

Eli Lilly pointed out that Axid was 20% cheaper than Zantac and 22% cheaper than Pepcid for 30 days treatment. The statement "An H2 antagonist that won't blow your budget" was reasonable given that the company said "an H2" rather than "the H2". The comments from Glaxo Wellcome regarding IMS sales information were misleading. Whilst the sales trend for H2 antagonists was flat, these agents and more specifically Zantac represented a large expense of both the health service and the individual general practitioner. Ranitidine was the second highest drug expense for the NHS in the general practice setting.

The advertisement supported the claim regarding "equally effective" with a specific reference. The company was not aware of data showing Zantac to be clinically superior to Axid nor of any data to show it to be better tolerated. Given the scale of use of both products clearly both had comprehensive safety information. There was no reference to the indications for each product, however the prescribing information gave full details of the indication for Axid. Given the fact that Axid and Zantac had comparable efficacy and safety in licensed indications, the big difference was indeed the price.

## FURTHER COMMENTS FROM GLAXO WELLCOME

Glaxo Wellcome queried whether it was acceptable within the spirit or the letter of the Code for a company to parody the visual devices and text from a competitor company's current advertising campaign, even if the claims made in the advertisement were acceptable. In the company's view it was not. Glaxo Wellcome pointed out it had made no complaint under Clause 9.3 of the Code. It did not believe that opinions gathered in the market research provided justification for such an activity.

Glaxo Wellcome maintained that the fact that over the last ten years Zantac had remained the world's most prescribed antiulcerant was one of the qualities of Zantac, the product that justified the description "fantastic" meaning "excellent" or "outstanding".

Glaxo Wellcome noted that Eli Lilly continued to

disparage Zantac by claiming that its development was "essentially an extension of research carried out earlier by other companies and researchers". Even if the company were to accept this to be true it was irrelevant since its "fantastic" success was undeniable. Eli Lilly had failed to provide any substantiation for the exaggerated claim that the cost of Zantac was "fantastic" whilst by implication the cost of Axid was not. Similarly Lilly had failed to provide any evidence to support the categorical and exaggerated claim that Axid was an "An H2 antagonist that won't blow your budget" but had merely restated the cost of 30 days treatment showing it to be cheaper.

Finally Glaxo Wellcome said that Lilly had not addressed its objection to the claim that Axid was "equally effective" and had "all the power" of Zantac. This clearly could not be the case as Zantac had more licensed indications and in the advertisement no specific indication was linked to the claim.

Glaxo Wellcome said that it was now apparent that Lilly intended to parody and disparage each Zantac advertisement in the current series and therefore the ruling of Appeal Board would have far reaching effects on the future direction of pharmaceutical advertising.

### APPEAL BOARD RULING

The Appeal Board first noted that Glaxo Wellcome had not made any allegations in its original letter of complaint about the claims in the advertisement at issue that Axid was "equally effective" and that "the big difference" was cost. These were first raised in Glaxo Wellcome's appeal. The Appeal Board could not rule upon these allegations as they had not formed part of the original complaint.

The Appeal Board then considered in general terms the use of parody in pharmaceutical advertising whereby a company reflected in its advertising the style or theme of another company's advertising. The Appeal Board considered that it would generally be difficult for companies to keep the use of parody in advertising within the requirements of the Code. It was the Appeal Board's view that it would not be in the industry's interest for the use of parody to become widespread and could envisage such activity deteriorating into abusive exchanges between competitor companies. Each case would, however, have to be judged on its merits.

In this particular instance, and bearing in mind Glaxo Wellcome's advertisement for Zantac, the Appeal Board agreed with the Panel's views. The Axid advertisement was not disparaging of Zantac. The Appeal Board did not accept that the implication that the cost of Zantac was fantastic was exaggerated or misleading, and the claim "An H2 antagonist that won't blow your budget" had been substantiated by Eli Lilly. The Appeal Board therefore upheld the all of the Panel's rulings of no breach of the Code.

The appeal therefore failed.

**Complaint received** **8 February 1996**

**Case completed** **24 April 1996**

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**CASE AUTH/399/2/96**

# GENERAL PRACTITIONER v WYETH

## Article in a newsletter

**A general practitioner complained about an article in Wyeth's specialist newsletter "change" alleging that it was misleading because it would be taken to refer to HRT trials carried out on Wyeth's product, Premique, whereas the trials described were on another company's product, Kliofem, which had different constituents.**

**The Panel considered that the newsletter had to be regarded as a promotional item. It was published by Wyeth and related to a therapeutic area in which the company had a product interest. The Panel noted that Premique was referred to in both editorial material and advertising and considered that readers would assume that the product referred to in the article was Premique, which was not so. The Panel therefore ruled that the article was misleading.**

### COMPLAINT

A general practitioner complained about an article appearing on the front page of Wyeth Laboratories' specialist newsletter "change" which discussed menopausal health. The article in question discussed the results from continuous combined hormone replacement therapy (HRT) trials performed by Dr David McKay-Hart at Stobhill Hospital in Glasgow and there were various quotes from his wife, Helen Hart, who was a menopause and research nurse working at his HRT clinic. These quotes were reputed to be from unpublished work from the trials which they had been conducting on continuous combined HRT. The article referred to the high level of patient satisfaction, the bleeding patterns that were reported, the weight loss that was reported and the reduced incidence of pre-menstrual syndrome.

The complainant had attended the 1995 British Menopause Society's Annual Symposium and had attended a satellite meeting run by Dr David McKay-Hart when he had presented some of the results of the many trials he had done with Kliofem, a Novo Nordisk product. The complainant was therefore perplexed to read about the continuous combined HRT trials in a Wyeth newsletter and he had reasoned that the new trials must be on the Wyeth continuous combined HRT, Premique, for which there was a full page advertisement on the back page of the newsletter.

The complainant had subsequently found out that Dr McKay-Hart's latest trials were in fact continuing his work on Kliofem. Kliofem and Premique contained

different oestrogen and progestogen components. The complainant therefore felt that it was wholly unacceptable to infer that the favourable trial results of Kliofem applied to Premique and alleged that Wyeth was deliberately trying to mislead general practitioners into believing that the Dr McKay-Hart trials pertained to Premique. The complainant believed that this was particularly the case as the trial work was yet unpublished and could not easily be checked. A breach of Clause 7.2 of the Code was alleged.

## RESPONSE

Wyeth Laboratories strongly refuted the allegation of deliberately trying to mislead the medical profession, the reasons being:

1 The article discussed the positive aspects of continuous HRT. No brand names were mentioned in the article or comparisons made.

2 Helen Hart was commissioned to write the article and had total editorial control. Full approval from Helen Hart and from Dr McKay-Hart, was obtained for the article to appear on the front page of "change".

3 Helen Hart's article and its contents were independent of any other article, text or advertising. Not only was there no intent to mislead but Wyeth failed to see how the article could be construed to be misleading.

4 Within this edition of "change", the only references to Premique were a full page advertisement and one sixth of a page launch announcement.

Wyeth stated that "change" was mailed to the medical profession via Doctor on 25 January 1996.

## RULING

The Panel considered that the newsletter "change" as a whole had to be regarded as a promotional item. It was published by Wyeth and related to a therapeutic area in which the company had a product interest. The newsletter was therefore subject to the Code.

The Panel noted that the front page of the newsletter included a flapper advertisement for Premique Cycle (a monthly bleed HRT) and an advertisement for Premique (a period free HRT) appeared on the back page. The flapper advertisement partly overlaid the article in question. There was also new product information relating to these products in the editorial material in the newsletter.

The Panel considered that given the nature of the publication, the fact that it was produced by Wyeth and that it referred to Premique both in the editorial material and in advertisements, readers would assume that the continuous combined HRT product in the trials was Wyeth's product Premique. This was not the case as the trials had been carried out on Novo Nordisk's product Kliofem. The Panel considered that the article was misleading as alleged as it failed to make it clear that the trials were on another product with different constituents. A breach of Clause 7.2 of the Code was ruled.

**Complaint received** **13 February 1996**

**Case completed** **2 April 1996**

CASE AUTH/401/2/96

# LEO v E MERCK

## Curatoderm press release

**Leo complained about two press packs, one for the lay media and one for the medical press, which referred to Curatoderm and were issued by E Merck. There were seven allegations.**

**The Panel considered that the lay press pack did not constitute advertising to the general public. The content was reasonable. Information on Curatoderm was given together with background information on psoriasis and other treatments. No breach of the Code was ruled.**

**The Panel ruled no breach of the Code with regard to a statement in a press release included in both press packs on the use of Curatoderm on the face. It was a general statement on the place of Curatoderm in psoriasis treatment.**

**The remainder of the allegations related to a press release which was only in the medical press pack. A breach of the Code was ruled in relation to a misleading statement which implied that Curatoderm was the only vitamin D product which could be applied to flexures and this was not true. A statement that "The tolerance of Curatoderm was excellent" was ruled in breach of the Code as it was an exaggerated statement and not capable of substantiation. The Panel did not accept that the press release would mislead prescribers into thinking that Curatoderm could be used continuously. Doctors would be familiar with the intermittent nature of the disease. No breach of the Code was ruled. The Panel ruled no breach with regard to a statement that the use of Curatoderm was "bound to improve compliance". Finally a price comparison of Curatoderm and calcipotriol (Leo's product, Dovonex) was alleged to be misleading as it had not been stated as to whether the comparison was with calcipotriol cream or ointment. The Panel ruled no breach of the Code as there was no price difference between the two presentations.**

### COMPLAINT

Leo Pharmaceuticals complained about press materials and other information about Curatoderm issued on behalf of E Merck Pharmaceuticals. The materials complained about by Leo were two press releases, one headed "Launch of new vitamin D analogue for psoriasis" and the other headed "New hope for psoriasis sufferers", pages entitled "Fact sheet on Curatoderm" and "Background information on psoriasis", the patient information leaflet and the summary of product characteristics (SPC). At the top right hand corner of all of these, except the patient information leaflet and the SPC, was a female face with two closed eyelids painted over, one with the sun and the other with moon. This image was being used throughout Merck's campaign.

Merck supplied copies of two press packs. Both were supplied in white folders with the "face" logo on the front. The first pack was for the medical press and contained the press releases "Launch of new vitamin D analogue for psoriasis" and "New hope for psoriasis sufferers" together with the pages headed "Factsheet on Curatoderm" and "Background information on psoriasis". All of these documents had the "face" logo on their top right hand corner. In addition the pack contained an SPC for Curatoderm. The second pack was for the lay press and contained only the press release "New hope for psoriasis sufferers" together with the pages headed "Factsheet on Curatoderm" and "Background information on psoriasis". No SPC was included. Neither press pack contained a patient information leaflet.

There were a number of allegations which were considered as follows:-

### 1 Advertising prescription only medicines to the general public

### COMPLAINT

Leo alleged that the press materials constituted advertising a prescription only medicine to the general public in breach of 20.1 and 20.2 of the Code.

Use of the coloured logo depicting a female face with the sun and moon eyes was derived from the prescription medicine advertisement and there was repeated use of the Curatoderm trade name throughout.

### RESPONSE

Merck said that the press release "Launch of new vitamin D analogue for psoriasis" was only given to members of the medical press and therefore could not be considered to be advertising to the public. Merck also disputed that the lay press pack given to patient groups and accredited medical/health correspondents for women's magazines constituted advertising to the public. The company said that although the press release did contain the image used in Merck's advertising, it had refused requests for the image to be reproduced in non trade journals and it therefore should not reach the general public. This practice of using the image associated with the advertising campaign on press packs was common practice.

The use of the word "Curatoderm" was no more frequent than was necessary in the context of what was written but it was impossible not to use it more than once when giving information about the product even when this was simply factual information. On average, the press release for the lay press used the word "Curatoderm" twice per page which compared favourably with the SPC in which it was used five times.

Use of the trade name rather than the generic name could not in itself be considered advertising. There was no generic form of the product giving limited advantage to the use of the trade name. Journalists were used to using the trade names which were generally easier than the generic names and more distinctive within the same class of drug leading to less confusion between products. If use of the trade name were in itself advertising, this would also be the case in the SPC which was of course freely

available to the public in the form of the compendium for leaflets and data sheets. This was of course not the case.

**RULING**

The lay press pack had to comply with the requirements of Clause 20 of the Code. In the Panel's view, it was not necessarily unacceptable to use a brand name or a brand image in lay press materials. The use of the generic name would not guarantee that the material was acceptable. The issue was whether the material overall met the requirements of Clauses 20.1 and 20.2 of the Code. The Panel noted that the lay press materials gave background information on psoriasis as well as detailed information about Curatoderm. Information was also included about other treatments. The Panel noted that it appeared that the SPC was not included in the lay press pack although the "Fact Sheet on Curatoderm" referred to the enclosed SPC.

Having examined the materials and what they had to say, the Panel decided that the lay press pack was not an advertisement for Curatoderm and therefore ruled no breach of Clause 20.1 of the Code.

The Panel decided that, on balance, the lay press pack was acceptable with regard to the requirements of Clause 20.2 that material must be factual and presented in a balanced way. There was not excessive use of product branding. The word "Curatoderm" only ever appeared in normal type face; it was never emboldened, nor had emboldened type face been used to emphasise any points within the lay press pack. The Panel did not consider that the lay press pack would encourage patients to ask their doctors to prescribe the product. The Panel therefore ruled no breach of Clause 20.2.

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Allegations 2 - 6 related to statements in the press release "Launch of a new vitamin D analogue for psoriasis". This press release formed part of the medical press pack and was not included in the lay press pack. Breaches of Clauses 7.2, 7.3 and 7.7 of the Code were alleged.

During the consideration of allegations 2 - 6 the Panel noted that medical press releases did not come under Clause 20 of the Code which dealt with information for the general public. Medical press releases were, in the Panel's view, subject to the general requirements of the Code.

## 2 "...Curatoderm, a new vitamin D analogue for the treatment of chronic plaque psoriasis as a first line agent for the management of this distressing disease"

**COMPLAINT**

Leo pointed out that chronic plaque psoriasis was, by definition, a chronic disease. Failure to point out that the use of Curatoderm was restricted to two courses of 8 weeks duration in any one year was seriously misleading.

**RESPONSE**

Merck stated that the fact that a medicine was given in courses rather than continually did not make it an ineffective treatment, nor inappropriate for a chronic disease nor inhibit it from being a first line treatment. Many of the "mainstays" of psoriasis treatment such as steroids, dithranol and UV treatment were given in intermittent courses. Also this condition, while chronic, was characteristically marked by periods of relapse and remission. Furthermore, the SPC was included with the medical press pack and this gave the restrictions of use of Curatoderm.

**RULING**

The Panel noted that the statement used the term "management" which, in the Panel's view, implied that treatment would be long term but not necessarily continuous. Given the incidence of psoriasis, prescribers would be familiar with its intermittent nature and the Panel ruled no breach of Clause 7.2 of the Code.

## 3 "Curatoderm ointment (tacalcitol) is the first once-daily vitamin D analogue treatment for psoriasis with the added advantage that it is gentle enough to use on the face and flexures unlike other currently available vitamin D analogues"

**COMPLAINT**

Leo pointed out that there was no published information comparing tacalcitol with other vitamin D analogues either on the face or flexures. The press release itself pointed out that comparative studies were needed. Furthermore, its product Dovonex could, for example, be used in flexure areas.

**RESPONSE**

Merck pointed out that the SPC for Dovonex (calcipotriol), unlike that for tacalcitol, stated that the product should not be used on the face. This was because calcipotriol could cause local irritation and this was a particular problem in those areas where the skin was more "delicate", such as the face.

Merck submitted that it was fair to make a distinction between the vitamin D analogues currently available, ie calcipotriol and Curatoderm, in this regard. With respect to the need for comparative studies of the local skin tolerance of both products on the face and flexures, such a study was problematic because of the ethics of applying Dovonex to the face and flexures when it was specifically warned against using it in this way. The data available, including the SPC for Dovonex, supported the distinction without a head to head comparison.

With regard to flexures, the generally held view among the profession was that the face and flexure areas went together as delicate areas where problems of drug induced irritation might occur. Merck quoted a number of studies to show that the literature did not support the use of calcipotriol on flexures.

**RULING**

The Panel noted that the Curatoderm SPC implied that it could be used on the face by the statement "When

applying to the face avoid contact with eyes". In contrast, the data sheet for Dovonex stated that the product should not be used on the face. Neither the data sheet for Dovonex nor the SPC for Curatoderm specifically recommended that either product should be used on flexures but such use was not contraindicated. The Panel therefore assumed that both products could be used on flexures. The statement in question was not true as Dovonex could be used on flexures. The Panel therefore ruled a breach of Clause 7.2.

## 4 "...the tolerance of Curatoderm was excellent..."

### COMPLAINT

Leo alleged that use of this superlative was not capable of substantiation.

### RESPONSE

Merck stated that "excellent" was not a superlative - the superlative would be "the most excellent"

Merck did not accept that the statement overstated the tolerance of Curatoderm. The study referred to in the press release showed that tolerance to Curatoderm was found to be comparable to placebo, even though patients received treatment to all of their lesions including on the face and flexures. This was an excellent result. The author of the study had approved the press release.

### RULING

The Panel noted that the published study included the statements "The tolerance of tacalcitol was judged to be comparable to placebo", "...the tolerance was good" and "...its extremely good tolerance". (Merck had also supplied another study by the same author, in manuscript form, which assessed the tolerance of Curatoderm but as Merck requested it remain confidential , and thus could not be made available to enquiries for substantiation, the Panel did not consider whether or not it provided further substantiation for the claim).

The Panel considered that the statement "the tolerance of Curatoderm was excellent" was exaggerated and not capable of substantiation given that the author of the study used the words "good", "extremely good" and that the tolerance was comparable to placebo. The product was a new product with limited data on side effects etc. The Panel ruled a breach of Clause 7.7 of the Code.

## 5 "Curatoderm holds an added bonus in that it can be used on the face and flexures and need only be applied once a day, which is bound to improve compliance"

### COMPLAINT

Leo said that Curatoderm was not the only treatment for psoriasis which could be used on the face and flexures. Furthermore the statement "Bound to improve compliance" was exaggerated.

### RESPONSE

Merck submitted that the statement which had been made by a representative of the Psoriasis Association did not imply that no other treatment could be used on the face and flexures; it was merely listing the benefits of Curatoderm.

The statement that, as it need only be applied once a day, it was "bound to improve compliance" was not an exaggeration. "Bound to" was not a quantitative term, it simply implied the inevitability of an improvement in compliance. It was widely accepted that a once daily dosage regime gave better compliance than a twice or thrice daily dose regime and there was a large amount of supporting data. This was particularly so with time-consuming topical applications which tended to get missed in the morning rush. It was important to highlight this issue in the press release as an item important to the quality of life of patients with this chronic disease.

### RULING

Although the statement was a quotation the Panel noted that it was not exempt from the provisions of the Code. The Panel did not accept that the statement implied that Curatoderm was the only product that could be used on the face and flexures. It was merely referring to a feature of Curatoderm. The Panel did not accept that the phrase was exaggerated and agreed that patients were more likely to adhere to a topical treatment regimen which had to be applied once daily than if it had to be applied more often. The Panel ruled no breach of the Code.

## 6 Price comparison

### COMPLAINT

The press release included a price comparison in the statement: "The NHS price for a 30g tube of once-daily Curatoderm ointment is £15.09. This compares favourably with the NHS price of £16.30 for a 60g tube of twice-daily calcipotriol". Leo pointed out that calcipotriol was prescribable as an ointment and/or cream. Failure to highlight this was misleading. Any prescription written for calcipotriol could not be filled by a pharmacist.

### RESPONSE

Merck pointed out that since the price of calcipotriol ointment was indentical to the price of calcipotriol cream for both the 60g and 120g tubes the company failed to understand how the ommission of the word ointment could mislead.

### RULING

The Panel noted that calcipotriol was available either as an ointment or as a cream but there was no price difference between the two presentations. The Panel did not consider that the statement was misleading and therefore ruled no breach of the Code.

## 7 Press release entitled "New hope for psoriasis sufferers" (in both medical and lay press packs)

### COMPLAINT

Leo pointed out that, according to the SPC, tacalcitol was degraded by sunlight and patients were advised to avoid exposure to sunlight whilst using Curatoderm. Emphasising use of this product in facial psoriasis was inappropriate and might raise unreasonable expectations on the part of both prescribers and patients.

### RESPONSE

Merck accepted that ultra violet light might cause some degradation of tacalcitol but it did not advocate that sunlight should be avoided when using this product. Indeed, the combination of tacalcitol with ultra violet light might be beneficial and the SPC mentioned this combination. Providing patients applied Curatoderm at night before they went to bed, as suggested in the SPC, efficacy was not affected.

The studies demonstrating the efficacy of Curatoderm were performed with night-time application and allowing patients to continue their normal daily activities, including going outside in the sunlight. This was the case where treatment of facial lesions was included and tacalcitol proved effective following this regime.

Curatoderm was efficacious when applied to the face or other parts of the body even if patients were exposed to sunlight, providing the application was at night.

The use of Curatoderm on the face was not emphasised. It was mentioned twice in the two pages. It was an important fact supported by both clinical data and the SPC.

### RULING

The Panel noted that Curatoderm could be used on the face and that the SPC advised applying the product at bedtime if the patient was likely to be exposed to sunlight. It was not unreasonable to refer to the use of Curatoderm on the face in the press release. As it was a general statement on the place of Curatoderm in the treatment of psoriasis the Panel considered that the press release was acceptable. The Panel therefore ruled no breach of the Code.

**Complaint received** **16 February 1996**

**Case completed** **11 April 1996**

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**CASE AUTH/404/2/96**

# LEO v E MERCK

## Curatoderm promotional item

**Leo complained about a Curatoderm promotional item issued by Merck. The item consisted of a folded A4 card and an attached pad of tear off leaflets entitled "Using the new psoriasis treatment". Leo alleged that the tear off leaflets constituted advertising to the public. Attention was drawn to two claims on the A4 card. Firstly, that the use of the word "the" in the claim "The once daily vitamin D3 for psoriasis" was in breach as it implied a special merit that could not be substantiated. Secondly the statement "Single application per 24 hours minimises ointment requirement, reducing costs" was alleged to be a hanging comparison.**

**The Panel noted that it was not clear whether the tear off leaflets were intended for the doctor or the patient. The leaflet would almost inevitably be given to patients prescribed Curatoderm. It was not an advertisement for a prescription only medicine and the content was reasonable for either a doctor or a patient prescribed Curatoderm. The Panel therefore ruled no breach of the Code which was upheld by the Appeal Board on appeal by Leo.**

**The Panel ruled that the claim "the once daily..." product was justified as Curatoderm was the only once daily vitamin D3 for psoriasis.**

**The Panel ruled that the statement referring to reducing costs would be taken as a comparison of the cost of using any ointment once daily with the cost of using that ointment twice daily. It did not accept that there was an implication that the statement related to the difference in cost between Curatoderm and Leo's product Dovonex as alleged. No breach of the Code was ruled. Following an appeal by Leo, the Appeal Board considered that the statement was misleading as it was too general and a breach of the Code was ruled.**

Leo Pharmaceuticals complained about a Curatoderm promotional item issued by E Merck Pharmaceuticals (ref ZZ02099 CT00495). The item consisted of a folded A4 card and a pad of tear off leaflets entitled "Using the new psoriasis treatment" was attached to the inside. There were three allegations which were considered as follow:

### 1 "Using the new psoriasis treatment" tear off leaflets

### COMPLAINT

Leo alleged that the leaflet was in clear breach of Clause 20.1 of the Code as it constituted advertising a prescription only medicine to the general public.

### RESPONSE

Merck said that the leaflet was not designed to be handed out to the patient - it was written for the health professional, primarily general practitioners. It was to be used as a reference, providing information that the doctor (or a dermatology nurse etc) might wish to give to a patient when they had received a first prescription for Curatoderm (tacalcitol). It could then be placed in the patient's notes as a reminder of the prescription and items discussed and so aid follow up.

The company submitted that the language in the leaflet made it quite clear to whom the leaflet was addressed.

The company cited the following examples: "An improvement in the look and feel of the skin may be noticed around two weeks, although this may vary from patient to patient" and "While it is not likely that patients will encounter any problems while using tacalcitol there are some simple precautions that should be taken so please advise your patient to read the detailed patient information leaflet...".

Even if the patient was shown a leaflet, this would only be appropriate following a prescription for Curatoderm. The contents of the leaflet were purely factual and non promotional in nature. Therefore this would still not constitute advertising to the public.

## PANEL RULING

The Panel noted that it was acceptable in principle for companies to produce material for patients. All material for patients needed to comply with Clause 20 of the Code. If material referred to a prescription only medicine then it could only be supplied to a patient after the doctor had decided to prescribe that product. Doctors needed to be given clear instructions about the use of such material, which had to be accompanied by prescribing information when provided to the doctor.

The Panel examined the leaflet and noted that it referred in detail to psoriasis and the use of tacalcitol.

At first sight the leaflet looked as if it was intended for the patient. This impression was reinforced by the title "Using the new psoriasis treatment" (emphasis added). Furthermore the language used was very basic. The Panel noted that the leaflet used phrases such as "your patient" or "from patient to patient" thus suggesting that the leaflet was in fact intended for the doctor.

The Panel noted that in its submission Merck said that the leaflet might be handed to a patient but it was not designed for such use. The Panel considered that the leaflet would almost inevitably be given to patients prescribed Curatoderm. There was no evidence that it had been given to patients who had not been prescribed Curatoderm. The Panel did not accept that in the circumstances the leaflet was an advertisement for a prescription only medicine as alleged. The content was reasonable for either a doctor or a patient prescribed Curatoderm. The Panel therefore ruled no breach of Clause 20.1 of the Code.

## APPEAL BY LEO

Leo said that although it was claimed that the leaflets were not designed to be handed out to the patient and were written for the health professional, two facts made this unlikely - the language in the leaflet was very basic and telephone numbers for Merck's Medical Information Department, the Psoriasis Association and the Psoriatic Arthropathy Alliance were provided in the leaflet. This, therefore, confirmed that patients would be given the leaflet.

The leaflet included the brand name, the product logo and the following promotional claims: "an improvement in the look and feel of the skin may be noticed in around two weeks" and "tacalcitol is potent".

Only leaflets enclosed in the container or package were exempt from the advertising regulations as stated in the Medicines Control Agency (MCA) Guidance for the Pharmaceutical Industry on the Labelling and Leaflets Regulations 1993. As the leaflet under question was product specific and promotional, this constituted advertising to the public and was in breach of Code.

The MCA had confirmed by personal communication that only factual, informative statements might be provided to the public. The product name should not be included and the MCA would want to review any such material prior to use.

## RESPONSE FROM MERCK

Merck said that the language in the leaflets was constructed to be understood by patients. This was deliberate and it did not imply that the leaflets were intended to be given to patients. Since the purpose of producing these leaflets was to provide guidance to the health professional on the sort of information they might wish to convey to a patient to whom they had given a first prescription of Curatoderm, providing the information in language suitable for the patient could only be considered an additional aid to the doctor. The provision of telephone numbers was also so that doctors could readily advise patients as to where further support was available.

In the event that the entire leaflet was given to a patient, consideration had to be given to the content. The company drew attention to the supplementary information to Clause 20.2 of the Code that "Companies may provide members of the health professions with leaflets concerning a medicine with a view to their provision to patients to whom the medicine has already been prescribed, providing that such a leaflet is factual and non promotional in nature".

Merck accepted the leaflet contained the brand name but there was no prohibition against this in the Code. The generic name was used throughout the leaflet, apart from the statement "for further information on Curatoderm, call our Medical Information help line on...". Merck submitted that it was particularly appropriate to use the brand name in certain circumstances.

As the patient would have already received a prescription for the product it was difficult to appreciate how such an appearance of the same name as on the pack would be promotional. The brand name would not promote a sale and therefore was not promotional.

Merck said that the face image from the advertising campaign was not a logo and in any case it would not promote requests for prescription of the product. In itself the image conveyed no information to the patient and had no association with the product for the public as they were not privy to the advertising campaign.

The claims cited by Leo that "An improvement in the look and feel of the skin may be noticed in around two weeks" was qualified in the the leaflet which stated that "An improvement in the look and feel of the skin may be noticed in around two weeks, although this may vary from patient to patient". Such selective editing by Leo clearly detracted from the meaning of the complete sentence. The statement was fair, balanced and factual. It conveyed important information to patients with this condition where both patient and doctor needed to have

some idea of how long to persist with treatment before they can expect to see an effect. It avoided an effective treatment being abandoned too early and an ineffective treatment being persisted with for too long.

Leo had also cited the claim "Tacalcitol is potent". In fact this appeared in the leaflet as "Like other medications used to treat psoriasis, tacalcitol is potent and should be used sparingly". Again, such selective editing was presumably an attempt by Leo to distort the meaning of the original sentence. The original sentence was likely to promote both reduced wastage and safe usage of the ointment by limiting the amount applied to any given area of psoriasis.

It was difficult to see how statements relating to a delay in the effect after starting treatment and a warning to use sparingly could be considered promotional. The leaflet was not promotional and contained only factual information. The reference by Leo to the Labelling and Leaflet Regulations was therefore misleading as they were only relevant to package leaflets.

#### FURTHER COMMENTS FROM LEO

Leo noted that Merck had stated that the language was constructed to be understood by patients. It seemed remarkable to follow this by the assertion that this did not imply that the leaflet was intended to be given to patients. This assertion was even more remarkable since the promotional item incorporated at least ten of the tear-off leaflets under discussion.

There was nothing in the reply from Merck which would lead Leo to change its view that promotional claims were made and as such constituted the advertising of a prescription only medicine to the public.

#### APPEAL BOARD RULING

The Appeal Board did not regard the leaflet in question as advertising to the patient and upheld the Panel's ruling of no breach of Clause 20.1.

The appeal on this point therefore failed.

### 2 Claim "The once daily vitamin D3 for psoriasis"

The claim appeared on the A4 card.

#### COMPLAINT

Leo alleged that the use of the word "the" in the claim was in breach of Clause 7.8 of the Code.

#### RESPONSE

Merck & Lipha submitted that while use of the word "the" in the claim might imply a special merit, the claim could be substantiated since Curatoderm was the only once daily vitamin $D_3$ for the treatment of psoriasis available in the UK.

#### PANEL RULING

The Panel noted that it was true that Curatoderm was the only once daily vitamin D3 for psoriasis. The other vitamin D3 product Leo's product, Dovonex (calcipotriol), was for twice daily use. The Panel considered that in the circumstances the use of the word "the" was justified and therefore ruled no breach of Clause 7.8.

### 3 Statement "Single application per 24 hours minimises ointment requirement, reducing costs"

The statement at issue appeared on the A4 card in a section headed "Once daily effectiveness and All over gentleness".

#### COMPLAINT

Leo alleged that the "costs" statement was a hanging comparison in breach of Clause 7.2 of the Code. Within the totality of the piece it was quite clearly implied that there were other vitamin D treatments available for psoriasis. This statement could be interpreted as "reducing costs" relative to Dovonex.

Any cost comparison or statement must take relative efficacy into account.

#### RESPONSE

Merck said that the statement was a complete sentence and was a statement of fact rather than a comparison. The sentence contained no comparative adjective which would imply comparison with an unstated noun.

Merck considered Leo to be aggrieved about the statement on the grounds that it could be taken to mean that Curatoderm was less expensive than Dovonex (calcipotriol). Since Curatoderm ointment was less expensive than Dovonex ointment, even if such an interpretation were possible, which Merck disputed, it would still be fair.

Curatoderm ointment was applied once a day and calcipotriol ointment was applied twice a day. The area of coverage achieved by an ointment would be similar for all ointments. Therefore, when comparing daily treatment costs, 2g of calcipotriol must be compared with 1g of Curatoderm.

The price of a 30g tube of Curatoderm was £15.09 compared with a 60g tube of calcipotriol which was £16.30 and the price of a 60g tube of Curatoderm was £26.06 compared with £29.40 for 120g tube of calcipotriol. These were comparable treatments for the same condition and therefore this was a fair comparison.

#### PANEL RULING

The Panel noted that the material featured on the once daily use of Curatoderm. In the Panel's view the statement at issue would be taken to be a comparison of the cost of using any ointment once daily with the cost of using that ointment twice daily. The Panel did not accept that there was a clear implication that the reduction of costs related to the difference between Dovonex and Curatoderm as alleged. In any event Curatoderm cost less than Dovonex. The Panel decided that in the circumstances the statement did not constitute a hanging comparison and therefore ruled no breach of the Code.

### APPEAL BY LEO

Leo said that "reducing costs" was indeed a hanging comparison. It did not accept that the claim would be accepted as a comparison of cost between using any ointment once daily and the cost of using that ointment twice daily. The basis of comparison was not clear.

Leo referred to the Panel's ruling in point 2 above. Leo said that as the claim "The once-daily vitamin D for Psoriasis" was in comparison with other vitamin D3 analogues, it was unacceptable that the claim "Single application per 24 hours minimises ointment requirement, reducing costs" was then considered to be an internal comparison within tacalcitol or a general statement applying to all medications.

The Panel's comment that "in any event, Curatoderm costs less that Dovonex" was irrelevant since it was well accepted that cost-comparisons could not be made without efficacy considerations.

### RESPONSE FROM MERCK

Merck said that no comparison was made nor intended and no mention of Dovonex or any other product was made in the text of the complete promotional item.

Merck said that cost was a very important issue in current medical practice ranking alongside efficacy and safety. This being so, it was rational to provide doctors with information on the daily treatment cost for a medicine. This was extremely difficult for this sort of a product where the area to be treated was so very variable and hence the amount used per application was so variable. One factor in the cost equation was how often the product must be applied. Since Curatoderm had the advantage of only requiring application once a day Merck wished to point out how this should be taken into account when considering the price.

### FURTHER COMMENT FROM LEO

Leo made no further comment on this point.

### APPEAL BOARD RULING

The Appeal Board considered that the use of the phrase "reducing costs" introduced an element of comparison as the cost of Curotoderm must be reduced compared to the cost of something else.

It was difficult to justify the statement as an general comparison between the costs of applying ointment twice a day compared to applying that ointment once a day. Had Curatoderm originally been launched for twice daily application and was now available as a once daily application then the statement might have been true. Curatoderm, however, was only available on a once daily basis.

The Appeal Board considered that it was misleading simply to state that Curatoderm reduced costs as this was not true, for example, in relation to topical steroids although it might be true in relation to the cost of Dovonex.

The Appeal Board considered that the statement was misleading as it was too general. The Appeal Board ruled a breach of Clause 7.2 of the Code.

The appeal on this point therefore succeeded.

**Complaint received** **21 February 1996**

**Case completed** **23 May 1996**

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**CASE AUTH/406/2/96** *NO BREACH OF THE CODE*

# UNIVERSITY DOCTOR v HOECHST MARION ROUSSEL

## Tarivid 400 mailing to general practitioners

**A university doctor complained about a mailing on Tarivid 400 sent to general practitioners by Hoechst Marion Roussel. The complainant alleged that a comparison of Tarivid 400mg with ciprofloxacin 500mg bd was misleading and oversimplistic. The widespread adoption of a 400mg daily dose of Tarivid would lead to underdosing, particularly in hospitals.**

**The Panel accepted that the complainant had provided some evidence to support the view that it was not possible to talk about equivalent daily doses of Tarivid and ciprofloxacin to cover all possible indications. The company had provided data to support its position. Given that the mailing went to general practitioners and referred to lower respiratory tract infections the Panel did not accept that it was unreasonable. No breach of the Code was ruled.**

**The Appeal Board upheld the Panel's ruling on appeal by the complainant.**

A reader in clinical pharmacology and infectious diseases at a university complained about a Tarivid 400 mailing (ref number 950904AW) sent by Hoechst Marion Roussel. The mailing included a cost comparison of Tarivid 400mg od and ciprofloxacin 500mg bd based on World Health Organisation (WHO) equivalent daily maintenance doses.

### COMPLAINT

The complainant said that the Tarivid promotional material had been brought to his attention by an employee of Bayer. The complainant was currently involved in a study funded by Bayer which addressed the important question of equivalent doses between quinolones. The complainant provided a copy of an abstract which summarised the results to date. The abstract referred to AUIC (AUC/MIC) ratios for the products. [AUIC = Area under the inhibitory serum concentration time curve, AUC = area under curve and MIC = minimum inhibitory concentration]. The project would be completed when *in vitro* MIC work on

representative strains had been finished. The complainant said that the results to date convinced him that it was not possible to talk about equivalent doses of ofloxacin (Tarivid) and Bayer's product ciprofloxacin (Ciproxin) to cover all possible indications. If ciprofloxacin and ofloxacin were being used predominantly to treat infections caused by gram negative bacteria then the 1000mg dose of ciprofloxacin was usually going to be equivalent to 800mg of ofloxacin and not 400mg. If, on the other hand, the products were being used to treat infections where gram positive organisms might be a problem, then the equivalent dose of ofloxacin might well be 400mg. Like many infectious disease physicians the complainant would not recommend either antibiotic to be used alone for the treatment of gram positive infections.

The complainant alleged that the mailing was misleading and over simplistic. His principal worry was that the widespread adoption of a 400mg daily dose of ofloxacin would lead to underdosing, particularly in hospitals. A claim in the material that ofloxacin was cheaper was also misleading because if you accepted the opinion about the equivalent doses, then hospitals or general practitioners would save more money by switching from 1000mg of ciprofloxacin to a daily dose of 500mg of ciprofloxacin.

## RESPONSE

Hoechst Marion Roussel pointed out that the material was a mailing sent to general practitioners who treated the majority of lower respiratory tract infections which was the only indication discussed in the mailing. The company recognised that although the normal dose of ofloxacin, which was clearly stated in the data sheet as 400mg daily for lower respiratory tract infection, had been found to be sufficient to treat the majority of patients for whom it was prescribed, there was a provision to increase the dose to 800mg daily for patients suffering more severe illness which was by its nature more likely to occur in a hospital setting.

The company was not aware of reports of frequently occurring treatment failures in patients treated according to its recommended dosing schedules for Tarivid 400. There were ample data to support the legitimacy and efficacy of a single 400mg daily dose of ofloxacin in lower respiratory infections (notably acute exacerbations of chronic bronchitis). A number of studies were provided.

The company pointed out that the complainant's research was not completed and not yet in the public domain. The work would appear to relate solely to *in vitro* data and to published pharmacokinetic values and therefore the company questioned how relevant the assumptions were to the clinical situation. The company was not aware of clinical data to support the hypothesis that the AUIC (AUC/MIC) values could be used to determine the clinical dosage equivalence of two agents. It was difficult to envisage the practical application of the hypothesis in the context of treating infections in general practice, where an assumption had to be made concerning likely pathogens and an appropriate antibacterial agent selected. The company respected the complainant's opinion but did not accept that it should be used in isolation to imply that the Tarivid 400 data sheet recommendations had led, or would lead, to underdosing or that the WHO "defined daily dosages" cited in the mailing were invalid. The defined daily doses were widely recognised and used as a legitimate standard for comparing drug costs.

There were ample data to illustrate the higher levels achieved by ofloxacin in blood, sputum and lung tissue compared to ciprofloxacin. These were all factors very relevant to considerations of clinical efficacy and dose equivalence.

The company submitted that these considerations supported the contention that in lower respiratory tract infections the most reasonable comparative dosages were ofloxacin 400mg od and ciprofloxacin 500mg bd, with higher doses of 400mg bd for ofloxacin and 750mg bd for ciprofloxacin being appropriate in the most severe infections.

## PANEL RULING

The Panel examined the mailing at issue which had been sent to general practitioners and not to hospital doctors. In the Panel's view it was not entirely clear that the aim of the mailing was to discuss lower respiratory tract infections as submitted by the company although the mailing did refer to "...a difficult chest infection...", "...prevalent respiratory tract pathogens...", "...common chest pathogens" and "...can alter the course of a difficult chest infection". The prescribing information on the back of the mailing gave the uses of Tarivid as lower respiratory tract infections, upper and lower urinary tract infections, uncomplicated urethral and cervical gonorrhoea and non gonococcal urethritis and cervicitis.

The Panel accepted that the complainant had provided some evidence to support the view that it was not possible to talk about equivalent daily dosages of ofloxacin and ciprofloxacin to cover all possible indications. This evidence was not in the public domain. It noted that Hoechst Marion Roussel had provided clinical data to support the claim that 1000mg of ciprofloxacin and 400mg of Tarivid could be considered to be equivalent doses in lower respiratory tract infections. This was further supported by the WHO defined daily dosages of ofloxacin as 0.4g and ciprofloxacin as 1g which did not specify any indication.

Bearing in mind that the mailing went to general practitioners, and not hospital doctors who would be treating more difficult infections than general practitioners, the Panel considered that at the present time the balance of the evidence supported the company's submission that 1000mg ciprofloxacin was equivalent to 400mg ofloxacin. The evidence submitted by the complainant was not sufficient to alter this view. The position might change in the future as more data became available.

The Panel ruled no breach of the Code.

## APPEAL BY COMPLAINANT

The complainant did not accept that the mailing was clearly restricted to lower respiratory tract infections (LRTI). If this were so then it should further distinguish between pneumonia, acute exacerbations of chronic bronchitis and cystic fibrosis because the range of pathogens and their relative susceptability to the two products were entirely different.

The complainant commented that Hoechst Marion Roussel relied on comparisons of defined daily doses (DDD). The complainant pointed out that the Nordic Council of Medicines warned that the defined daily dose meant the assumed dose per day for the drug used in its main indication in adults. DDD then was not the same thing as recommended dose, nor necessarily the dose actually used and in comparison of price per DDD of medicines belonging to the same category it was important to observe significant clinical differences which might mean that the drugs were not interchangable.

The complainant commented that Hoechst Marion Roussel had accepted that there were important kinetic differences between ofloxacin and ciprofloxacin but did not concede that there was ample published evidence to support the view that ciprofloxacin was consistently more potent than ofloxacin with respect to killing or inhibition of growth of gram negative bacteria. Two previous studies had shown that the superior absorbtion of ofloxacin might be offset by the superior antibacterial potency of ciprofloxacin. The differences in kinetics and antibacterial potency, both of which were potentially important clinically, meant in the words of the Nordic Council of Medicines that ciprofloxacin and ofloxacin were not interchangable.

The complainant noted that Hoechst Marion Roussel was dissatisfied with the clinical evidence supporting the AUIC ratio as a method for comparing doses of quinolones. Hoechst Marion Roussel stated that the concept was based on one dose ranging study for ciprofloxacin. The complainant considered that the model concurred with the results of a second dose ranging study on community acquired cystitis. Hoechst Marion Roussel conceded a crucial point that no such studies had been undertaken with ofloxacin. Although the AUIC of ofloxacin had not been formally examined, one of the papers supplied by Hoechst Marion Roussel compared various doses of ofloxacin for treatment of exacerbations of chronic obstructive airways disease (COAD) and concluded that it appeared that both the bacteriological and the clinical results of the treatment of recurrent respiratory infection were better when ofloxacin was given in 800mg doses once daily for seven days and the higher ratio of the maximum sputum concentrations of ofloxacin to the MICs of the *S pneumoniae* strains that were cultured was almost certainly the explanation for this. The appropriate empirical dose therefore should be decided on the basis of the sensitivity of the likely infecting pathogen, in addition to clinical severity. Given that *S pneumoniae* was a likely pathogen in most community acquired LRTI, the complainant alleged that it was misleading to suggest that the 800mg daily dose should only be a reserved for patients whose infections were more severe on clinical grounds.

The complainant did not expect to reach consensus about precisely equivalent doses of ciprofloxacin and ofloxacin for all indications. The complainant acknowledged that there was a woeful lack of clinical dose ranging studies particularly for ofloxacin. The point was precisely that. The drugs were clearly not equivalent according to the criteria of the Nordic Council of Medicines and therefore in the absence of evidence from clinical trials it was misleading to suggest that there was proven equivalence between two dosing regimens across all types of LRTI.

The complainant commented that Hoechst Marion Roussel was not aware of any reports of frequently occurring treatment failures in patients treated with 400mg of ofloxacin and that Mulholland had not noticed any problems after the substitution of ofloxacin 400mg for ciprofloxacin 1g in Glasgow. The Appeal Board should be aware that neither of these reassurances was compelling. With respect to exacerbations of COAD, the advantages of antibiotic treatment could be demonstrated in well designed placebo controlled randomised clinical trials and the benefits confined to about a third of patients who had the greatest clinical evidence of infection. That was why the complainant was not reassured by the type of equivalence studies submitted in support of the 400mg ofloxacin dose for the treatment of exacerbations of COAD. The complainant doubted whether any differences would have been demonstrated between the antibiotic regimens and placebo. The only dose ranging study submitted by Hoechst Marion Roussel supported an 800mg daily dose not a 400mg daily dose. Similarly Bayer was only able to prove that the doses of 200mg bd of iv ciprofloxacin should be increased to 400mg bd through carefully controlled clinical trials. Claims for doses should be based on comparative clinical dose ranging trials not anecdotal and observational data. The experience with iv ciprofloxacin and the fact that clinicians had been forced to accept that they had been dosing aminoglycosides suboptimally for decades showed that complacency about clinical practice should not be used as evidence.

The complainant alleged that the mailing was misleading as it was not clear that it was specifically about LRTI and even then it should specify exactly which type of LRTI was being considered. There were important pharmacological differences between ofloxacin and ciprofloxacin which meant that dosing equivalence should not be based on comparison of defined daily doses. If the Appeal Board rejected the AUIC ratio as a method for estimating dose equivalence then the only valid alternative was head to head randomised dose ranging studies. The appropriate dose of any quinolone depended on the likely pathogens in addition to the clinical severity of the infection.

## RESPONSE FROM HOECHST MARION ROUSSEL

Hoechst Marion Roussel said the mailing clearly referred on several occasions to chest infections. It was targeted at general practitioners who treated patients in the community in the absence of a definitive diagnosis of either the precise nature of the infection or the infecting pathogen. The statement "With difficult chest infections" in the mailing was a term understood and used by general practitioners and would be taken to refer to such infections as exacerbations of chronic bronchitis which the company viewed as one of the limited roles which quinolones had in the community.

A consensus was unlikely to be reached across all possible indications for Tarivid and ciprofloxacin regarding precisely equivalent dosages and indeed a recent Drug and Therapeutics Bulletin acknowledged this point in stating that interdose comparisons and comparisons between drugs at different dosages were scarce and the minimum effective dose seemed to be poorly defined, which would affect cost comparisons. In the mailing the

company sought to draw attention to price differences between ciprofloxacin and ofloxacin when used in broadly comparable dosages for chest infections. The dosage comparison was reasonable and in the absence of head to head randomised dose ranging clinical studies, the dosage range quoted reflected both the mid range point of the licensed dosages for the two products in question and the WHO defined daily dosages. These DDDs might be imperfect markers but they did at least provide a starting point for doctors to assess relative costs and were frequently so used. Given that general practitioners were unlikely to know the identity and sensitivity of the pathogens involved and hence have to treat empirically rather than according to AUICs the company did not believe that selection of such markers was unreasonable or misleading.

Sales data supported the impression that in primary care the most commonly prescribed dosages were 1000mg per day of ciprofloxacin and 400mg per day of ofloxacin. This did not constitute grounds for saying that the two products were clinically equivalent but did support the reasonableness of the price comparison.

Hoechst Marion Roussel acknowledged that in the future the AUIC might be seen as a useful tool for comparing different antibacterial agents; however, at present, the evidence for such use was limited. The complainant's own study which specifically addressed the issue of comparable doses for ofloxacin and ciprofloxacin had not yet appeared in the public domain and therefore could not form part of the company's deliberations when considering its mailing which it believed reflected both the current state of scientific knowledge and the product licence.

The company believed that as Tarivid 400 was licensed as a once daily therapy in LRTI it was not unreasonable to select this dosage for the basis on which to make a price comparison and physicians would consider ciprofloxacin 500mg bd as a reasonable comparative dose.

## FURTHER COMMENTS FROM THE COMPLAINANT

The complainant pointed out that Hoechst Marion Roussel conceded that the reference to sales figures and defined daily dosages did not constitute grounds for saying that the two products were clinically equivalent but the company then went on to say that this did support the reasonableness of the price comparison. The complainant repeated that usual practice was not evidence for effectiveness.

The complainant noted that Hoechst Marion Roussel conceded that there were insufficient clinical trials to provide definitive equivalent doses for ofloxacin and ciprofloxacin and other sources of evidence must be used. The complainant provided a paper by Madras-Kelly *et al* which compared the dose responses of ciprofloxacin and ofloxacin against two strains of *Pseudomonas aeruginosa*. The final paragraph of the abstract corroborated the point that the undoubted pharmacokinetic advantages which ofloxacin had over ciprofloxacin might be offset by differences in antimicrobial potency. Once this was conceded then it followed that the debate about equivalent doses must include information about the relative potency of the two products against their most likely pathogens for each infection which was to be considered.

The complainant did not accept the argument that GPs did not know the bacteria causing the infections which they were treating. In hospital and community practice empirical antibiotic treatment was based on a knowledge of local epidemiology. The bacteria which were most likely to cause exacerbations of chronic bronchitis were not the same as those which were likely to cause community acquired pneumonia. The question of relative doses for exacerbations of COAD should focus on the relative susceptibility of *Haemophilus influenzae* whereas for pnemonia the focus should be on *Streptococcus pneumoniae* and the causes of atypical pneumonia. For *H influenzae* the equivalent doses of ofloxacin and ciprofloxacin were likely to be similar whereas for *S pneumoniae* the equivalent doses of ciprofloxacin maybe two fold higher than the dose of ofloxacin.

The complainant accepted that GPs might well use a term "difficult chest infections" and understand what it meant to them but was there any evidence that all GPs meant the same thing by this vague term? The issue of definition of clinical severity was exceedingly complex and encompassed the virulence of the infecting pathogen, its sensitivity to antibiotics, the site of infection and the vulnerability of the patient. It was grossly oversimplistic to suggest that serious debate about equivalent doses could be founded on such woolly terminology as "difficult chest infections". Exacerbations of COAD and pnuemonia were both difficult to treat but were caused by different pathogens located at different sites which would require quite different dosing strategies for quinolones.

The complainant considered that it was depressing how often good quality papers in peer reviewed journals supported the use of antibiotics at doses which were higher than those promoted. It would be sad if the ABPI endorsed a promotion which was based on current prescribing habits rather than scientific evidence.

The complainant was adamant that any debate about equivalent doses of quinolones must make reference to the bacteria which were most likely to cause the infection. Hoechst Marion Roussel had provided no evidence to refute that argument.

## APPEAL BOARD RULING

The Appeal Board was concerned that the complainant's attention had been drawn to the mailing by an employee of Bayer. If Bayer was worried about the mailing it should have complained direct to the Authority.

The Appeal Board accepted that the mailing referred to chest infections by the use of phrases such as "difficult chest infections" and "the usual daily dose of Tarivid 400 penetrates to the sputum...". It noted that the mailing had been sent to general practitioners.

The Appeal Board accepted that there would be difficulties in using WHO defined daily doses to compare products. Each case would have to be judged on its merits. It noted that in this instance there was no indication specified.

The Appeal Board considered that it was not unreasonable to compare a dose of 400mg of Tarivid with 500mg bd of ciprofloxacin. The doses used were typical

licensed doses and these would be used by a GP to treat difficult chest infections. The general practitioner intitiating such a treatment would not generally be aware of the pathogens causing the infection.

The Appeal Board upheld the Panel's ruling of no breach of the Code.

The appeal therefore failed.

**Complaint received** 23 February 1996

**Case completed** 23 May 1996

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**Case AUTH/409/3/96**

# ETHICS COMMITTEE CHAIRMAN v SERVIER

## Cardiovascular risk evaluation

**The Chairman of a research ethics committee complained about a cardiovascular risk evaluation being carried out by Servier, alleging that it was of limited scientific value and that its main objective was to familiarise general practitioners with Servier's name.**

**The Panel noted that Servier had already discontinued the study because it realised that some elements could be interpreted as promotional. The papers relating to the study included promotional material for Natrilix, a Servier product. The Panel considered that the association of such a study with promotion was unacceptable and ruled the study in breach of the Code.**

### COMPLAINT

The chairman of a research ethics committee complained about a cardiovascular risk evaluation study in a hypertensive population being carried out by Servier Laboratories Ltd. The committee alleged that the study was of very limited scientific value and was concerned that the main objective was to familiarise general practitioners with the name of the sponsoring company rather than to pursue any serious scientific question. In the circumstances, the committee had felt unable to give approval for the study to proceed.

### RESPONSE

Servier, although not a member of the ABPI, had nevertheless agreed to comply with the Code.

Servier said that the study was originally designed to recruit 612 cases from 204 centres as widely distributed throughout the United Kingdom as possible. Recruitment commenced in July 1995 and by late November Servier had identified 97 general practitioners who were interested in participating in the study and who would have recruited less than half of the intended number of patients. At this time, Servier realised that there were elements in the study which might be interpreted by some as promotional. It was therefore decided in-house not to proceed with further recruitment.

However, Servier had already received some positive feedback indicating that some GPs had gained significant insight into their patients' health which they would not have obtained otherwise. This was primarily the result of the echocardiography investigation which was not normally part of the routine clinical screening in hypertensive patients and in at least two patients this had led to the revision of the overall diagnosis and treatment which was to the patients' benefit. Other GPs had indicated their enthusiasm for the opportunity to undertake more in-depth assessments than might otherwise have been the case. Given this kind of response and the commitment Servier had made to physicians who wished to participate, it felt obliged to honour its agreements but to cease any further recruitment.

Therefore, from late November 1995 no further centres had been recruited but Servier had assisted in the preparation of ethics committee applications for GPs who had indicated their wish to participate before that date. There was no promotional benefit to be gained by following this course of action but Servier felt that it was supporting improved clinical diagnosis.

However, as a result of the problems that had now arisen regarding the Code, Servier had decided to stop the study and inform the GPs and ethics committees involved.

In conclusion, Servier said that it had initiated the study in good faith and when it realised that it was possibly in breach of the Code it took the necessary steps to halt recruitment three to four months before any complaint was made. The subsequent action which it had taken also indicated its clear wish not to be in default.

### RULING

Before the Panel was the pack which had been supplied to each participating centre. This contained the study protocol, the financial protocol, study reporting documentation, an electronic cardiovascular risk calculator and a data sheet for Natrilix, a diuretic for the treatment of hypertension marketed by Servier.

Also before the Panel were copies of the letters sent to the participating doctors and ethics committees about the discontinuance of the study and the letter sent to those GPs who had made their own application to their respective ethics committees informing them of Servier's decision to withdraw the study.

The Panel noted that the evaluation was an epidemiological study aimed at assessing the prevalence of multiple coronary risk factors in a randomly selected group of hypertensive patients, newly diagnosed or already receiving treatment. Each participating general practitioner was to recruit three patients who were suffering from essential hypertension, regardless of

whether they were newly diagnosed or receiving antihypertensive therapy or whether they had any co-existing disease states. General practitioners would be paid £250 per patient but this fee was to include the cost of all investigations in the protocol which included measurements such as blood pressure, blood and urine tests, an ECG and an echocardiogram.

The Panel noted that patients on antihypertensive therapy entering the study were not to have their treatment changed and that newly diagnosed patients would receive treatment at the discretion of the prescriber, independently of the study. There was thus no obligation to use Natrilix or any other of Servier's products in order to participate. The Panel noted, however, that a folder in which case report forms were enclosed was promotional in nature. It had the appearance of promotional material, Natrilix was mentioned on all four pages with claims for the product on pages 2 and 3 and what amounted to a full page advertisement on the back cover. The cardiovascular risk calculator provided bore the name Natrilix and the instructions for its use also referred to Natrilix. A data sheet for the product had also been supplied.

The Panel considered that the association of the study with promotional material was totally unacceptable. If a study carried out by a pharmaceutical company was to have any credibility whatsoever, it had to be completely separate from any activity of a promotional nature. This was not so in the present case.

The Panel noted that Clause 10.2 of the Code required that clinical assessments and the like must not be disguised promotion. The Panel considered that the study in question was unacceptable given the requirements of Clause 10.2 and it thus followed that the payments made to participating general practitioners were also unacceptable. Breaches of Clauses 10.2 and 18.1 of the Code were ruled.

**Complaint received** **7 March 1996**

**Case completed** **18 April 1996**

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**CASE AUTH/410/3/96**

# E MERCK v LEO

## Dovonex press materials and "Dear Doctor" letter

**E Merck complained about press materials and a "Dear Doctor" letter for Dovonex issued by Leo.**

**A gram for gram price comparison of Dovonex with tacalcitriol (Curatoderm) in the press material was ruled to be misleading as no account had been taken of the licensed usages of the product.**

**The second allegation concerned statements comparing the calcaemic potential of Dovonex and tacalcitriol which appeared both in the press material and the "Dear Doctor" letter. The Panel ruled that both statements were misleading in breach of the Code as the clinical relevance of the differences in this regard was not clear and too much significance had been given in the circumstances. It had not been made clear in the press material that the statement was derived from animal data.**

E Merck Pharmaceuticals complained about a press statement to the medical press headed "Dovonex - High Clinical Efficacy Supported by Extensive Documentation" and a "Dear Doctor" letter sent by Leo Pharmaceuticals.

The allegations were considered as follows.

### 1 "Tacalcitol ointment is 60% more expensive than Dovonex Ointment and Cream (60 g £26.06 vs 60 g £16.30)" (appearing in press statement)

#### COMPLAINT

Merck said that Leo had compared gram for gram of ointment when the equivalent dosage requirement for the same indication was 2 grams of Dovonex Ointment for 1 gram of tacalcitol ointment (Curatoderm). In fact, when examining the daily treatment cost for Curatoderm, Dovonex Ointment was more than 7% more expensive than Curatoderm. A breach of Clause 7.2 was alleged.

#### RESPONSE

Leo said that data were available on the comparative efficacy of Dovonex applied once daily and tacalcitol once daily. These data showed clearly that the efficacy of the two drugs used once daily was similar, although with a trend in favour of Dovonex. When similar doses of the two products were used they showed similar efficacy. Therefore, a gram for gram comparison of the price was valid, relevant, did not mislead and was substantiated by the data.

#### RULING

The Panel noted that Leo had calculated the relative cost of Dovonex and Curatoderm assuming that the dose was the same for both products. This was not the case. According to the Dovonex data sheet the product should be applied twice daily while the summary of product characteristics (SPC) for Curatoderm stated that the ointment should be applied, sparingly, once daily. Consequently, the Panel thought that comparing the costs of the two products only on a gram for gram basis was not a fair comparison, given that Dovonex was licensed for use twice daily and that Curatoderm was licensed for use once daily. The cost comparison took no account of the inevitable variability in usage rates but the Panel thought it not unreasonable to assume that a patient using Dovonex twice daily would apply twice as much ointment than if they used Curatoderm once daily.

The Panel considered that the cost comparison was misleading as no account had been taken of the licensed usages of the products and therefore ruled a breach of Clause 7.2 of the Code.

## 2 "Pharmacologically tacalcitol is 50 to 100 times more calcaemic than Dovonex" (appearing in press statement)

### COMPLAINT

Merck pointed out that the statement had been derived from a study where rats were given high oral and intravenous doses of a series of vitamin D3 analogues. The statement took no account of:

- the pharmacodynamic and pharmacokinetic differences between rats and humans
- differences in kinetics between oral and topical dosing
- differences between the clinically relevant dose and the doses used in the study
- differences between absorption of the various analogues through human skin (less than 0.5% of tacalcitol is absorbed)
- the fact that the clinically equivalent dose of Dovonex Ointment was 25 times greater than that of Curatoderm Ointment - one gram of Dovonex Ointment contained 50 micrograms of calcipotriol and was applied twice a day, while Curatoderm contained 4 micrograms of tacalcitol and was applied once a day.

Merck said that the statement by Leo was designed to mislead in such a way as to discredit the safety of the Merck product. A breach of Clause 7.2 was alleged.

With regards to the misuse of this data, Merck also drew attention to a "Dear Doctor" letter, dated March 1996, which again implied that Curatoderm was more likely to produce hypercalcaemia in patients than Dovonex.

The "Dear Doctor" letter contained the statement "Dovonex aims for maximum efficacy with a concentration of 50 mcg/g of calcipotriol applied twice-daily without the need to monitor calcium levels. Tacalcitol, however, only contains 4 mcg/g of its active ingredient and should be applied in the evening to avoid degradation by UV light. A pharmacological animal study has confirmed that molecule for molecule tacalcitol is 50 to 100 times more calcaemic than calcipotriol."

### RESPONSE

Leo said that the statement issued to the press referred to the pharmacology of vitamin D analogues and was clearly referenced to the journal, Pharmacology and Toxicology. No clinical conclusions or inferences were made within the statement and, therefore, the statement was not misleading.

With regard to the "Dear Doctor" letter Leo said that it included the statement "A pharmacological animal study has confirmed that molecule for molecule tacalcitol is 50 to 100 times more calcaemic than calcipotriol". This clearly stated the Leo position and did not mislead in any way.

### RULING

The Panel considered that the comparison in the press statement of the calcaemic potential of the two products was too brief. It had not been qualified or put into context in any way and it was not obvious that the statement had been derived from animal data. The clinical relevance of the statement was not apparent. The Panel noted, from the relevant data sheet and SPC, that both Dovonex and Curatoderm were contraindicated in patients with known disorders of calcium metabolism and that both products could precipitate hypercalcaemia in certain patient groups.

With regard to the "Dear Doctor" letter, the Panel noted that it was sent only to dermatologists. Although the information regarding the calcaemic nature of Dovonex and Curatoderm was more comprehensive than in the press statement, it was preceded by a paragraph "The ultimate aim of a topical psoriasis treatment should be to offer maximum efficacy with minimum side-effects". Placing the statement about calcium levels immediately after a paragraph about minimum side effects might lead the reader to assume that, compared to Curatoderm, hypercalcaemia was not a problem with Dovonex. According to the warnings in the Dovonex data sheet this was not necessarily true. The Panel accepted that the tacalcitol molecule was 50 to 100 times more calcaemic than the calcipotriol molecule but it noted that the differences in strength and dosage of the two products (tacalcitol 4 micrograms per gram applied once a day and calcipotriol 50 micrograms per gram applied twice daily) would erode this difference. In any case the clinical significance of the difference in calcaemic potential between the two products was not clear. Although the "Dear Doctor" letter stated that the data had been derived from animal studies the Panel considered that in the absence of any direct clinical relevance, too much significance had been attached to the data.

The Panel considered that the statements relating to the relative calcaemic potential of Dovonex and Curatoderm in both the press statement and the "Dear Doctor" letter were misleading and therefore ruled each in breach of Clause 7.2 of the Code.

**Complaint received** **13 March 1996**

**Case completed** **19 April 1996**

CASE AUTH/412/3/96

# SCHWARZ v BAYER

## Cost comparison chart in Adalat advertisement

**Schwarz Pharma Ltd alleged that a cost comparison chart in a journal advertisement for Adalat issued by Bayer which compared the costs of a number of products at the usual maintenance dose was unfair as it did not contain any products which were less expensive than Adalat LA30, such as Schwarz's product Plendil. Furthermore, it was not clear which indication was being discussed as some of the products listed were licensed for both angina and hypertension and one of the products, lacidipine, was licensed for hypertension only.**

**The Panel ruled that the cost comparison chart was misleading as the basis for the selection of products was not stated and the impression was given that all the products listed could be used to treat both hypertension and angina and this was not so.**

### COMPLAINT

Schwarz Pharma Limited complained about an "advertorial" featuring the Adalat LA range of Bayer plc Pharmaceutical Division which appeared in issue No. 5 of Healthcall News Review (issued January 1996) sent to 5000 GPs. The advertisement at issue was headed "Money Matters" and consisted of several paragraphs of text headed "Improved therapy for hypertension and angina at a lower cost", a cost comparison chart showing daily treatment costs for a range of cardiovascular products and prescribing information for Adalat LA.

Schwarz said that whilst the text of the article discussed comparisons between two Bayer products, Adalat LA and Adalat Retard, the cost comparison chart showed a range of products. The table showed Adalat LA as the least expensive product of those listed. However, Schwarz believed that this was an unfair representation as Bayer failed to show less expensive products such as Schwarz's product Plendil 5 mg (felodipine).

Furthermore, Schwarz believed that the chart was ambiguous and possibly misleading as it did not make clear the intended indications for treatment. Given the text of the advertisement it could be construed that all the drugs shown in the chart were licensed for both angina and hypertension. This was not the case as lacidipine was only licensed for the treatment of hypertension. Schwarz alleged that the advertisement was in breach of Clause 7.2 of the Code.

### RESPONSE

Bayer said that the advertisement focused on the comparison between Adalat LA and Adalat Retard and the cost comparison was designed specifically to highlight the cost advantages of the newer formulations of its own products. To put this into context, Bayer had therefore included a number of more recently licensed products commonly used to treat hypertension..

Currently, felodipine was only prescribed to a relatively small proportion of patients and lay 30th in the ranking prescriptions issued (approximately 0.25% of scripts for hypertension compared to 13.5% of scripts for nifedipine). Bayer believed the cost comparison showed a reasonable selection of those products most often used by the physician. Bayer provided IMS prescription share data relating to the hypertension market. This ranked 51 products according to the percentage of prescriptions written for them.

Bayer said that if it had included all agents with similar market share to that of felodipine, the table would have included up to 30 products which would have rendered the table cumbersome and confusing. Due to the number of products available, Bayer had no alternative but to be selective. It maintained, however, that it had selected a fair and reasonable collection of more recently launched comparative products.

Bayer said that as it was not incumbent upon it to include all competitors in a clinical comparison, it believed that it was not bound to include all competitors in a cost comparison. In relation to the second item of Schwarz's complaint, Bayer emphasised that this was primarily a cost comparison and not a clinical comparison. It considered that its main responsibility was to supply prescribing information and recommendations for its own products and did not accept that physicians sought or expected clinical advice from Bayer in relation to competitor products.

### RULING

The Panel noted that the price comparison chart compared the daily treatment costs of nine products, three of which were different forms of Adalat - LA30, LA60 and Retard. Adalat LA30 was shown as the least expensive option. Other products in the chart were the ACE inhibitors captopril, enalapril and lisinopril, and the calcium channel blockers diltiazem LA, lacidipine and amlodipine.

Given that the market share data supplied by Bayer had included 51 products, it was not unreasonable for the costs of only selected ones to be shown. The Panel considered, however, that where a selection had been made, then the basis for selection should be stated and should be fair. The chart was headed "cost comparison" and was based on usual maintenance doses but no basis for the selection of the products given. The Panel noted that in its response Bayer had variously stated that the basis for selection was " ...more recently licensed products commonly used to treat hypertension", " ...those products most often used by the physician" and "...more recently launched comparative products".

The Panel considered that it was unclear whether the basis for selection had been the more recently launched products or those most often used. The Panel queried whether the products could be regarded as recently licensed products. In addition, from the market share data supplied, it was clear that the two agents most often used,

one a diuretic and one a beta-blocker, had been excluded from the chart. The Panel did not think that the exclusion of Plendil from the chart was unreasonable given its very small market share and therefore ruled no breach of the Code in that regard.

The Panel noted that the cost comparison chart was next to the headline which read "Improved therapy for hypertension and angina at a lower cost". It would be reasonable for readers to assume, therefore, that the agents listed in the chart could be used for both indications. This was not the case. All of the products listed could be used for hypertension but not all for angina. The chart did not state what indication was being examined.

The Panel considered that the cost comparison chart was misleading as the basis for selection of products was not clear and the impression given that the products in the chart could be used to treat both hypertension and angina was not true. A breach of Clause 7.2 of the Code was ruled.

**Complaint received** **20 March 1996**

**Case completed** **29 April 1996**

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**CASE AUTH/414/3/96**

# GENERAL PRACTITIONER v BRISTOL-MYERS SQUIBB

## Dutonin journal advertisement

**A general practitioner alleged that a visual in a Dutonin advertisement of a man flying an aeroplane, issued by Bristol-Myers Squibb, was inconsistent with the data sheet which stated that patients should be cautioned about driving.**

**The Panel ruled that the advertisement was in breach of the Code as the visual detracted from the data sheet warning. There was no acknowledgement in the advertisement that patients should be cautioned about driving.**

### COMPLAINT

A general practitioner complained about a journal advertisment for Dutonin issued by Bristol-Myers Squibb Pharmaceuticals Ltd. The advertisement featured a close-up aerial view of a man flying a light aeroplane. The complainant was concerned that the visual was inconsistent with one of the warnings given in the data sheet for the product:

"Effect on Ability to Drive and Use of Machines: In healthy volunteers Dutonin caused a modest decrease in some psychomotor function tests but no impairment of cognitive function. However, any psychoactive drug may impair judgement, cognitive or motor skills and patients should be cautioned about operating hazardous machinery, including automobiles".

Further, there was no acknowledgement of this advice given in the advertisement.

### RESPONSE

Bristol-Myers Squibb said that the advertisement for Dutonin was meant to represent an amusing image. Indeed this was demonstrated during market research testing of the advertisement and in subsequent anecdotal remarks from general practitioners. There was no intention on its part to suggest that this was a realistic scenario for anyone, let alone a depressed person on medication.

Bristol-Myers Squibb had been contacted by a GP who had voiced his concerns about the advertisement. Although it was absolutely not the company's intention to mislead in any way, the very fact that this GP had raised this point had already led Bristol-Myers Squibb to add a line to the advertisement to point out the labelling of Dutonin ie consistent with the use of any antidepressant drug that there were precautions against operating heavy machinery and automobiles whilst on therapy. Bristol-Myers Squibb had notified the GP to that effect.

### RULING

The Panel noted that the prescribing information included in the advertisement contained the warning "Modest decrease in some psychomotor function tests but no impairment of cognitive function". The data sheet for the product added a second sentence to this warning "However, any psychoactive drug may impair judgement, cognitive or motor skills and patients should be cautioned about operating hazardous machinery, including automobiles". By the omission of the second half of the warning prescribers might be misled into assuming that they had no need to caution their patients about driving. The visual of a man flying a light aeroplane might serve to reinforce this assumption.

The Panel noted that while the visual might be an unusual situation for most patients to find themselves in, it was not totally unrealistic. The text below the visual said that "Shortly after he started to take Dutonin, Paul had an overwhelming desire to travel through the air at great speed. Which was great because it was proof that he was making a good recovery from depression". This scenario was not too far removed from that of a patient wanting to get out and about in his or her car. No acknowledgement that patients should be cautioned about driving was included in the advertisement. The Panel considered that the visual detracted from the warning in the data sheet and ruled a breach of Clause 7.6 of the Code.

**Complaint received** **21 March 1996**

**Case completed** **24 April 1996**

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CASE AUTH/418/4/96

# WYETH v NOVO NORDISK

## Kliofem mailing

**Wyeth Laboratories complained about a Kliofem mailing sent by Novo Nordisk. Wyeth alleged that claims relating to post menopausal women's preference for period-free hormone replacement therapy were misleading as there was no data to substantiate such claim. Secondly, Wyeth alleged that a graph and a claim "Kliofem: Early resolution of bleeding" was misleading as it suggested that the graph was comparing Kliofem with another HRT formulation when in fact this was not the case.**

**The Panel noted its decision in a previous case, Case AUTH/396/2/96, in which the Panel had ruled that claims that Kliofem was the period-free HRT that post menopausal women preferred were ambiguous and not capable of substantiation as there were no data to substantiate the interpretation that women preferred Kliofem to other bleed free preparations. The Panel considered that these rulings applied similarly in the case now before it. The Panel ruled that the appearence of the graph below claims for Kliofem was misleading as given the layout of the leaflet and the positioning of the graph below a claim for Kliofem, readers would assume that the comparison was between Kliofem and another continous combined HRT product and this was not so.**

Wyeth Laboratories submitted a complaint about a Kliofem leaflet (ref KL196/6) distributed by Novo Nordisk Pharmaceuticals Ltd. Novo Nordisk was not a member of the ABPI but had nevertheless agreed to comply with the Code.

There were two allegations which were considered as follows:-

### 1 Claims relating to post menopausal women's preference for period free HRT

#### COMPLAINT

Wyeth drew attention to two statements in the leaflet, "Which is the period-free HRT that postmenopausal women prefer?" and "The word is out: Kliofem is period-free HRT that postmenopausal women prefer". Wyeth alleged that the statements clearly implied that of the period-free products available, Kliofem was the product which women preferred. However, the information to substantiate the statement merely made the case for period-free products generally versus monthly bleed/no HRT and made no comparison between Kliofem and the other currently available period-free products available such as its product Premique, and Climesse and Livial. Wyeth alleged that the material was misleading in breach of Clauses 7.2 and 7.8 of the Code.

#### RESPONSE

Novo Nordisk said that this allegation was similar in substance to Case AUTH/396/2/96. The Panel had ruled breaches of Clauses 7.2 and 7.3 of the Code in that case and this had been accepted by the company. The mailing in question in Case AUTH/418/4/96 had been sent between its response to the previous complaint and the receipt of the Panel's ruling.

#### RULING

The Panel noted its decision in Case AUTH/396/2/96 that claims that Kliofem was the period-free HRT that post menopausal women preferred were ambiguous and not capable of substantiation. Breaches of Clauses 7.2 and 7.3 of the Code had been ruled. The Panel considered that these rulings applied similarly in the case now before it.

### 2 Graph below the claim "Kliofem: Early resolution of bleeding"

#### COMPLAINT

Wyeth pointed out that the claim was supported by a graph comparing two progestogens added to conjugated oestrogens. This was alleged to be misleading as it suggested that the graph was comparing Kliofem (2mg oestradiol/1mg norethisterone acetate) with Premique (0.625mg conjugated oestrogens/5mg medroxyprogesterone acetate). Kliofem did not contain conjugated oestrogens and doses of progestogens stated in the graph were not contained in either Kliofem, Premique or in any other HRT formulation. The claim and graph were not a fair representation and breaches of Clauses 7.2 and 7.6 were alleged.

#### RESPONSE

Novo Nordisk submitted that the claim "Kliofem: Early resolution of bleeding" was substantiated by two items. Firstly, data on file showed that more than 80% of over 1000 UK women were amenorrhoeic or had acceptable light spotting at 3 months. Secondly, the statement which appeared immediately above the graph that "NETA offers a slightly quicker time to amenorrhoea compared to MPA" was taken from a study which was provided.

Novo Nordisk said that the graph was an exact copy from the paper except that it had removed the levonorgestrol part of the graph so as not to confuse the issue. The graph in the original paper was only labelled according to the content of progesterone whereas in the leaflet the company had specified that it was looking at a combination of conjugated oestrogens plus either medroxyprogesterone acetate (MPA) or norethisterone (NET). This labelling was added to ensure that the graph would not be misleading. It was well known that induction of amenorrhoea in continuous combined therapy was driven by the appropriate dose of progesterone in relation to oestrogen. The quoted study demonstrated that when the oestrogen was constant any variation of progesterone could be used to assess the efficacy of that component as a combination in inducing amenorrhoea. The principle that both type and

dose of progesterone influenced induction of amenorrhoea was demonstrated in many studies. Two studies were provided. The graph in question represented the only study comparing NET and MPA in a continuous combined regimen. The graph clearly showed a slightly quicker time to amenorrhoea in the group receiving norethisterone.

Novo Nordisk said that the graph was an exact copy of the graph in the paper and the presentation was clear, graphically accurate, to scale with no missing data or scale points.

With respect to the doses of progesterone used, the MPA dose of 2.5mg was exactly half that included in Wyeth's continous combined product, Premique, whereas the NET dose of 0.35mg was less than half of the NETA content in Kliofem. If anything the study was biased towards MPA as a relatively high dose of MPA was used as a comparator. Looking at the points with respect to amenorrhoea the graph was relevant to the claim being made.

### RULING

The Panel examined the graph in the leaflet and noted that it appeared beneath the claim "Kliofem: Early resolution of bleeding". Adjacent to the graph was the statement that the products in the study were conjugated oestrogens plus either medroxyprogesterone acetate 2.5mg or norethisterone 0.35mg. The line in the graph itself for norethisterone was in the same blue colour as the headings to the various sections of the leaflet. The Panel considered that readers of the material would assume that the blue line on the graph referred to results with Kliofem and this was not so. Kliofem did not contain conjugated oestrogens and the quantity of progesterone was 1mg as opposed to 0.35mg as shown in the graph. The dose of medroxyprogesterone in Premique was 5mg. The Panel decided that given the layout of the leaflet and the positioning of the graph below a claim for Kliofem, readers would assume that the comparison was between Kliofem and another continuous combined HRT product and this was not so. The Panel therefore ruled that the appearance of the graph below claims for Kliofem was misleading in breach of Clause 7.2 of the Code. The Panel noted that it should have been made clear in the leaflet that the graph had been adapted from the original paper.

**Complaint received** **16 April 1996**

**Case completed** **4 June 1996**

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**CASES AUTH/420/4/96 AND AUTH/422/4/96**

# DIRECTOR/SCRUTINY & MEDICINES CONTROL AGENCY v NORTON HEALTHCARE

## Journal advertisements for an inhaler

**A matter arising from the routine scrutiny of journal advertisements which could not be settled was referred to the Code of Practice Panel as a case in accordance with the Constitution and Procedure. The Medicines Control Agency (MCA) complained about a similar advertisement. The advertisements in question did not give a product name but both referred to the use of inhalers. In the journals in which the advertisements appeared, full advertisements for Baker Norton's Easi-Breathe inhalers, Beclazone and Salamol also appeared.**

**The Panel considered that neither of the advertisements at issue was a teaser advertisement as, in the Panel's view, a teaser referred to something that was not yet available. The Easi-Breathe inhalers were already available. The Panel considered that as the advertisements clearly related to Baker Norton inhalers each should have included prescribing information for one of the medicines or have been made into an abbreviated advertisement. The Panel ruled a breach of the Code as prescribing information had not been included.**

### Case AUTH/420/4/96

### COMPLAINT

This case arose from the routine scrutiny of journal advertisements. As the matter could not be settled, it was referred to the Code of Practice Panel as a case in accordance with Paragraph 17.4 of the Constitution and Procedure.

The advertisement in question appeared in Pulse, 9 March 1996. The black and white advertisement appeared on a right hand page and included a photograph of a man and a woman with the statement "Asthmatics using press-and-breathe inhalers may not be getting the most out of life..." above the photograph. Underneath the photograph the question "Can you afford to help them?..." appeared. In the top left hand corner there was a silhouette representing somebody using an inhaler. No company name was given. The next right hand page in the journal was an advertisement for Easi-Breathe inhalers issued by Baker Norton which included a photograph of a similar, or possibly the same, man and woman and included prescribing information for Beclazone and Salamol breath operated inhalers. The advertisement was predominantly black and white with the inhaler device, the words "Salamol" and "Easi-Breathe" in blue and the words "Beclazone" and "Easi-Breathe" in brown. It was pointed out to Norton Healthcare Limited that the first advertisement was considered to be an advertisement for Easi-Breathe inhalers and was in breach of Clause 4.1 as no prescribing information had been provided.

### Case AUTH/422/4/96

### COMPLAINT

The Medicines Control Agency (MCA) complained about an advertisement which appeared in Financial Pulse, 8

April 1996, picked up during its routine scrutiny. The MCA alleged that the advertisement was in breach of Clause 9.1 of the Code. The advertisement was slightly different to the one raised by the Authority in Case AUTH/420/4/96. The advertisement at issue in Case AUTH/422/4/96 used the same woman and man as in the first advertisement in Case AUTH/420/4/96 but included a little more text discussing the use of inhalers together with a photograph of a blue inhaler. The majority of the advertisement was in black and white apart from the company name, quotation marks and the inhaler device, which were blue. A second advertisement sent by the MCA was similar to the second advertisement referred to in Case AUTH/420/4/96 above.

**RESPONSE**

Norton Healthcare did not accept that either of the advertisements were teasers. It referred to the supplementary information to Clause 9.1 which stated that teaser advertising whereby promotional material was intended to "tease" the recipient by eliciting an interest in something which would be following or would be available at a later date without providing any actual information about it was not acceptable. The company presumed that the MCA was concerned that it was attempting to alert interest in Salamol and Beclazone Easi-Breathe. Both products were, however, already licensed, available and the subject of legitimate promotions. This would beg the question as to why Baker Norton or indeed any company in a similar position would need to resort to "teaser" advertising.

The company did not accept that the pieces were advertisements for any medicine and as such lay outside the scope of the Code as defined in Clause 1. The company drew attention to the exemptions under Clause 1.2 referring to "statements relating to human health or diseases provided there is no reference either direct or indirect to specific medicines". There was clearly no reference made to any specific product marketed by Baker Norton or indeed any other company. The object was to remind health professionals that the lifestyle of some asthmatics might be compromised by their failure to use press-and-breathe metered dose inhalers correctly. The message could as easily be taken to support the use of other companies' inhalers such as dry powder inhalers which Baker Norton did not market. It was therefore impossible to include any specific prescribing information when no specific medicine was mentioned or implied. The company submitted that this was similar to the legitimate advertising by pharmaceutical companies promoting only a corporate identity or research interest in a particular disease condition or as in this case to impart specific non-product related information about a disease condition and its treatment.

**RULING**

The Panel accepted that neither advertisement at issue was a "teaser" advertisement as defined under the supplementary information to Clause 9.1 of the Code. In the Panel's view, a "teaser" advertisement referred to something that was not yet available. The Easi-Breathe inhalers were available from Baker Norton and this was communicated to health professionals in the full advertisement for the Easi-Breathe products which contained prescribing information and appeared on the next right hand page in Pulse. The advertisement in question in Case AUTH/420/4/96 could not be part of a two page advertisement as it was separated from the Easi-Breathe advertisement containing the prescribing information by editorial text. The advertisements at issue in both cases were clearly linked to the Easi-Breathe campaign. The advertisements were predominantly black and white with limited use of blue for product names and the illustration of the inhaler device and the company name and the use of brown for a product name.

The Panel did not accept that the advertisements in question were exempt from the Code. They were paid for by Baker Norton and, by the use of negative statements, to the effect that patients derived little benefit from press-and-breathe devices, and the questions raised about the cost of alternative inhalers, could be taken as promotion of inhalers other than press-and-breathe such as Baker Norton's Easi-Breathe inhalers. The clear impression from the advertisements was that Baker Norton made an inhaler which was not a press-and-breathe device and was not expensive. The Panel considered that the advertisements clearly related to Baker Norton inhalers and each should have included prescribing information for one of the medicines or been made into an abbreviated advertisements complying with Clause 5 of the Code. As the advertisements were not abbreviated advertisements and neither included prescribing information, the Panel ruled a breach of Clause 4.1 of the Code in each case. This ruling would apply whether or not a full advertisement appeared later in the journal. No breach of Clause 9.1 was ruled.

**Case AUTH/420/4/96**

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| **Proceedings commenced** | **15 April 1996** |
| **Case completed** | **20 May 1996** |

**Case AUTH/422/4/96**

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| **Complaint received** | **25 April 1996** |
| **Case completed** | **4 June 1996** |

# MEDICINES CONTROL AGENCY v PROCTER & GAMBLE

## Didronel PMO "Dear Doctor" letter

**The Medicines Control Agency alleged that the objective of a letter sent by Procter & Gamble was to knock alendronate (Merck Sharp & Dohme's product Fosamax) and promote its product, Didronel. The letter addressed the gastrointestinal (GI) tolerance of Didronel compared to that of alendronate.**

**The Panel noted that the Merck group had issued material in the UK, America and Canada which referred to the upper GI side effects experience with Fosamax as being a class effect of bisphosphonates. The Panel noted that Didronel was the only other product in that class licensed for osteoporosis. It considered that, given the evidence, it was not correct to extrapolate from experience with the recently launched product alendronate and make a general statement in relation to all bisphosphonates. It was not unreasonable for Procter & Gamble to write to doctors about the situation and its implication for Didronel. The "Dear Doctor" letter was reasonable and not disparaging. The Panel therefore ruled no breach of the Code.**

### COMPLAINT

The Medicines Control Agency (MCA) complained about a Didronel PMO "Dear Doctor" letter sent by Procter & Gamble Pharmaceuticals. The letter addressed the issue of the gastrointestinal tolerance of Didronel compared to that of alendronate (Merck Sharp & Dohme's product Fosamax). The basis of the complaint was that the objective of the letter was to "knock" alendronate and promote Didronel PMO. The MCA did not think that the letter was misleading. A breach of Clause 2 was alleged.

The Authority also drew Procter & Gamble's attention to Clauses 7.2, 8.1 and 9.1 of the Code.

### RESPONSE

Procter & Gamble emphasised that the "Dear Doctor" letter should not be looked at in isolation. It was necessary to consider it in the context of the scientific background and chain of events which preceded it.

The letter was written to ensure that doctors would not be confused about whether Didronel was implicated in the serious gastrointestinal ("GI") side effect problem experienced with Fosamax which had led Merck & Co in the USA, Merck Frosst in Canada, and Merck Sharp & Dohme in the UK, to issue a "Dear Doctor" letter, warning doctors about this. The letter from the Merck group had, in every case, suggested that these GI side effects were a class effect of bisphosphonates, a class of products which, other than Fosamax, only included Didronel for the treatment of osteoporosis.

Procter & Gamble had experienced no such problems with Didronel and also had independent scientific evidence to demonstrate that this was not a class effect and was therefore not related to Didronel. Didronel was the most widely prescribed treatment for osteoporosis and was the only other bisphosphonate with a UK marketing authorisation in this therapeutic area. Procter & Gamble was aware that doctors and patients were confused by the publicity surrounding this problem and, given its market profile, was concerned that there was a high risk of Didronel being wrongly implicated in this safety alert. That risk was accentuated by the way in which Merck had sought to portray the effect experienced by its product as being characteristic of the class. Procter & Gamble therefore sent the "Dear Doctor" letter in question to clarify the issue and reassure doctors of the upper GI safety profile of Didronel. This could only be explained by referring to the GI issue identified by Merck & Co in relation to alendronate which was being widely reported in the press.

Didronel PMO, was first marketed in the United Kingdom in January 1992 for the treatment of established vertebral osteoporosis and contained etidronate, a bisphosphonate compound. Alendronate sodium (Fosamax) had been marketed in the UK by Merck Sharp & Dohme since September 1995 for the treatment of post-menopausal osteoporosis. Unlike etidronate, alendronate sodium was an amino-bisphosphonate. Nevertheless, the fact that the products both belonged to the bisphosphonate class had led many doctors and patients to see them essentially as alternative treatment options for the authorised indications. As one would expect, since the launch of Fosamax, there had been some switches in prescription between the two brands.

A number of bisphosphonate compounds had been developed. Some of these, like alendronate and pamidronate (but not etidronate), had an amino group attached to the basic molecule and there was good scientific evidence to suggest that it was the addition of the amino side chain which was related to the reported incidence of severe gastrointestinal side effects. For example, Francis referred to the higher incidence of serious gastric side effects associated with amino-bisphosphonates. In parallel with the problems reported with alendronate, pamidronate, which had a close structural similarity to alendronate, had been associated with a number of cases of severe oesophagitis (which had led to its discontinuation in oral form). In a recent review article, Adami and Zamberlan had said that the likeliest cause of this effect was oesophageal contact with undissolved crystals of amino compounds.

In summary, scientific and clinical evidence demonstrated that it was not correct to extrapolate from experience with alendronate and make a general statement in relation to all bisphosphonates. The statements that were issued by the Merck group only properly referred to the position of all *amino*-bisphosphonates. In view of this, Procter & Gamble felt it was entirely reasonable for it to clarify this issue and reassure physicians of its product's safety profile in this respect.

On 15 March, Merck & Co in the USA issued to specialist doctors a warning that there had been a number of reports of severe oesphagitis and ulceration with its

product Fosamax. This was followed by an identical letter sent to primary care physicians and other hospital doctors and a general press release and a letter to pharmacies. A letter in the same terms was sent to doctors and pharmacists in Canada by Merck Frosst Canada Inc. Procter & Gamble understood that, of the 211 oesophageal reactions associated with Fosamax, 36 cases required hospital admission. The letters contained amended instructions for the administration of the product. They also contained the statement:-

*"Like other bisphosphonates, however, FOSAMAX was recognised to have the potential to cause local irritation of the upper gastrointestinal mucosa."* (emphasis added)

Procter & Gamble considered that this statement did not accurately represent the scientific position. No such side-effect profile had been observed with Didronel and accordingly, as Merck's statement had to be viewed as referring to etidronate (as the only other approved oral bisphosphonate in the USA), a complaint had been filed with the Food and Drug Administration (FDA) by Procter & Gamble's affiliate in the USA.

Inevitably, very many reports concerning the release of the Merck letter and the controversy surrounding it began to appear in the international press and then the UK press. It also came to Procter & Gamble's notice that, in the UK, Merck Sharp & Dohme were following a similar course. In late March, Merck Sharp & Dohme issued a letter to UK specialists with a particular interest in the field referring to this suggested upper GI class effect (in substantially the same terms as the letter issued in the USA and Canada) and saying that all doctors in the UK were shortly to be notified of the problem. This UK correspondence was reported to Procter & Gamble by doctors who questioned the validity of Merck Sharp & Dohme's statements.

As publicity began to grow and more reports appeared in the specialist and lay press, Procter & Gamble was concerned that there was a substantial risk that the misconception promoted by Merck's letter that Didronel was also implicated in the side effect problem would take root. In view of the fact that Didronel was the most widely prescribed treatment for osteoporosis in the UK, there was a considerable risk that a large number of patients might have become concerned unnecessarily and inappropriately discontinued or been withdrawn from Didronel PMO therapy which might have had adverse effects upon their general health. A report in The Daily Telegraph, published the same weekend as the "Dear Doctor" letter in question was sent out, generated several enquiries from patients taking Didronel PMO who wanted to know whether their medication was implicated and had similar side effect problems to those reported. The problem of reports concerning one product in a class spilling over and affecting others was well known, particularly these days where lay media interest in health issues was so much greater than it was few years ago.

It was clear to Procter & Gamble that the controversy surrounding the side effects profile of this class of products would intensify with the delivery of a letter from Merck Sharp & Dohme to all remaining UK doctors. Had Procter & Gamble not written to doctors to clarify the situation, it was absolutely sure that a great deal of confusion would have developed and it would have had a flood of professional and public enquiries. Any action taken after the event rarely proved as effective as pre-empting it. Procter & Gamble therefore decided that the most appropriate and practical way to deal with this was to write to doctors providing them with evidence to reassure them that there was no such safety problem with Didronel PMO.

Procter & Gamble was aware now, of course, that the second letter which Merck Sharp & Dohme eventually sent out on 19 April to all remaining doctors did not contain the class effect statement. In the company's view this had much to do with the "Dear Doctor" letter which it had sent in the interim, but, in any event, any letter of this nature would lead to questions regarding extrapolation of the problem to other products in the class and Procter & Gamble believed it was entitled to address the issue to avoid further confusion and concern provided, that what was said was factual, fair and capable of substantiation. Procter & Gamble submitted that it had acted reasonably in contacting doctors, to inform them of the scientific position. The company had taken great care not to mislead as the MCA had conceded and had not received any complaints from the health care professions regarding either the form or content of its letter. In contrast, Procter & Gamble believed that the Merck group acted unreasonably, both in the USA and Canada and in its initial UK letter in referring to the problem as a class effect with bisphosphonates when there was clear evidence to the contrary.

Procter & Gamble noted that a breach of Clause 2 was an extremely serious matter and that this clause was reserved for circumstances where there was evidence of particularly reprehensible behaviour on the part of a company, such that the reputation of the industry as a whole was discredited. The company could not see any justification for saying that its action had been anything other than reasonable. The MCA said that the objective of the letter was to "knock" alendronate and promote etidronate. This was not the company's objective and it was not a reasonable interpretation of its letter. Procter & Gamble could not see how it could be said to be "knocking" alendronate when all it was doing was referring doctors to a warning that the Merck group itself had issued and which had been widely covered in the media in the UK and the USA about reported side effects with its product.

The purpose of the letter was to point out that what Merck Sharp & Dohme had described was not a class effect and to explain to doctors that etidronate and alendronate were different chemical entities, with different upper GI side effects, and to provide evidence to reassure them that Didronel had a good upper gastrointestinal safety profile. This was supported by data relating to the use of the product over 2.1 million patient years of exposure. This figure represented 18 years of treatment with etidronate world-wide for osteoporosis and other bone diseases. It represented 1.8 million patient years of the former and 0.25 million years of the latter. The figures had been calculated following ICH and CIOMS-II guidelines, on the basis of shipment data.

Procter & Gamble did not consider that it was disparaging either the activities or products of Merck Sharp & Dohme. It had explained the upper gastrointestinal side effect profile of Didronel in a way that was capable of total substantiation and had explained factually by direct

quotation why the company was obliged to address the issue. Disparagement at its lowest level involved an unfair comparison based upon false statements. Nothing here was false.

Procter & Gamble was aware that all materials issued to medical professionals must recognise the professional standing of those persons and comply with the requirements as to suitability and taste. It considered that its letter fully complied with this requirement, since it referred to a matter of genuine scientific concern and dealt with this in a perfectly straightforward manner. Procter & Gamble did not consider that either the form or content of the letter could be said to offend doctors in any way.

**RULING**

The Panel noted that it had not been provided with copies of the two letters sent by Merck Sharp & Dohme to UK doctors. According to Procter & Gamble's submission, the first letter had been sent in late March to UK specialists and referred to the upper GI side effects as a class effect of bisphosphonates in similar terms to the letters issued in the USA and in Canada which had been provided to the Panel. The second letter had been sent to all other UK doctors on 19 April but, according to Procter & Gamble's submission, had not contained the class effect statement. The Panel noted that the Didronel PMO "Dear Doctor" letter was dated 13 April and had been sent before the Merck Sharp & Dohme letter to all UK doctors (other than the specialists).

The Panel noted that the Merck letters sent in the USA and Canada stated that "Although infrequent, the reports of esophagitis/ulceration have generally been of a more severe nature than observed in either previous clinical trials or ongoing studies of Fosamax". Given the warnings about Fosamax sent to doctors and the fact that some of the correspondence referred to the GI side effect as being a class effect, the Panel did not consider that it was unreasonable for Procter & Gamble to write to doctors about the situation and its implication for Didronel. The information issued by Merck Sharp & Dohme had appeared in The Daily Telegraph and was bound to appear in medical journals etc distributed in the UK. The Panel noted that a patient on Didronel had contacted Procter & Gamble after reading about the problems with Fosamax in The Daily Telegraph.

The issue now to be considered by the Panel was whether the content of Procter & Gamble's "Dear Doctor" letter was reasonable.

The Panel noted that exposure to Didronel had been much greater than that to alendronate. Didronel was first marketed in the UK in January 1992. Fosamax was first marketed in the UK in September 1995. The current data sheet for Didronel contained the statement under the heading "Side effects Gastro-intestinal" that "In clinical studies of 2-3 years duration the incidence of these events were comparable to placebo. The most common effects reported in order of incidence were diarrhoea, nausea, flatulence, dyspepsia, abdominal pain, constipation and vomiting". Given the data and experience with etidronate, the letter was not unreasonable. The letters issued by Merck in the USA and Canada and by Merck Sharp & Dohme in the UK had the potential to damage Didronel by linking the serious upper GI problems to the bisphosphonate class of products. The Panel considered that the "Dear Doctor" letter issued by Procter & Gamble was an accurate and fair representation of what had been said about Fosamax. The Panel did not believe that the letter disparaged either Merck Sharp & Dohme or its product and nor did it bring discredit upon, or reduce confidence in, the pharmaceutical industry. The Panel therefore ruled no breach of the Code.

**Complaint received** **25 April 1996**

**Case completed** **25 June 1996**

CASE AUTH/424/4/96 *NO BREACH OF THE CODE*

# HOSPITAL PHARMACIST v RHONE-POULENC RORER

## Menorest promotional aid consisting of a Lubri Gel dispenser

**A hospital pharmacist complained that a promotional aid consisting of a Lubri Gel dispenser issued by Rhone-Poulenc Rorer had not complied with the hospital rules for the distribution of medicines. It was also alleged that the use of the brand name "Menorest" on the dispenser misled as to the nature of the item.**

**The Panel noted the company's submission that Lubri Gel was a device and not a medicine. Consequently, as Lubri Gel was not a medicine, it could not be a sample as defined in the Code as a small supply of a medicine. The requirements in the Code for samples (Clause 17) did not therefore apply. The Panel considered that the use of the name "Menorest" on the dispenser would not mislead as to the nature of the item given that the word "Menorest" was immediately followed by the explanation "This dispenser contains Lubri Gel for internal examinations". The Panel ruled no breach of the Code.**

### COMPLAINT

A hospital pharmacist complained about the promotion of Menorest transdermal patches by Rhone-Poulenc Rorer Limited. The item in question was a dispenser labelled "Menorest This dispenser contains Lubri Gel for internal examinations".

The complainant was concerned about the distribution of samples of Menorest Lubri Gel in the hospital. The pharmacy became aware of the product only when it received a request for information on whether it could be used with dinoprostone gel. On receiving this request and obtaining a sample of the product, the medical information department at Rhone-Poulenc Rorer was contacted. It was unaware of the product and that it was being used to promote Menorest transdermal patches. A request for the representative to contact the hospital, providing details as to where the product was distributed and in what quantity, received no reply. Five dispensers had been returned to the hospital pharmacy department. The complainant was concerned that the distribution of the dispenser, although presumably intended as a gift, represented the supply of a medicine. Distribution of medicines by representatives was forbidden and all samples had to be left with the pharmacy. A copy of the hospital policy was provided. Distribution of the Lubri Gel dispenser had not complied with the hospital requirements. A breach of Clause 17.8 of the Code was alleged.

Secondly, the complainant alleged that the product was in breach of Clause 18.2 of the Code as the name of the medicine being promoted, Menorest, was used on a promotional aid when it was inappropriate to do so and misled as to the nature of the item, suggesting that the product was Menorest Lubri Gel. Finally, the complainant pointed out that no ingredients were listed on the product and no expiry date was given.

### RESPONSE

Rhone-Poulenc Rorer Limited submitted that the item in question was an inexpensive plastic pump action container providing a convenient means of dispensing a lubricating gel for use in clinical examinations. It had been supplied as an aid to clinical practice, primarily to general practitioners with a few dispensers being made available in gynaecology clinics. The same gel had been provided by other pharmaceutical companies on a similar basis. The dispenser was one item used in the current promotion of Menorest to clinicians involved in the treatment of menopausal problems and thus carried the product logo. The dispenser was clearly labelled as containing Lubri Gel, with the Menorest logo being distinctly separate from this labelling.

Lubri Gel was classified as a medical device and not as a medicinal product. Consequently, its distribution was not in breach of Clause 17.8 of the Code since the distribution had not contravened the hospital's policy which specifically applied to the distribution of medicinal products. In addition, the lack of an expiry date on the container, noted by the complainant, reflected the lack of a quoted shelf life for Lubri Gel provided by the manufacturer.

The company accepted that, as a matter of courtesy, it would have been appropriate to inform the pharmacy of its activities and it had taken steps to deal with this oversight.

### RULING

The Panel noted that the response from the company stated that Lubri Gel was a device and not a medicine. The Panel noted that the Code applied to the promotion of medicines and that Clause 1.3 defined a medicine as any branded or unbranded medicine intended for use in humans which required a marketing authorization. Consequently, as the product was not a medicine, it could not be a sample, defined in Clause 17 of the Code as a small supply of a medicine. Clause 17 did not therefore apply. The Panel therefore ruled no breach of Clause 17.8 of the Code.

Rhone-Poulenc Rorer had been distributing the item as a promotional aid and therefore Clause 18.2 was relevant. The Panel noted that the dispenser was labelled "Menorest. This dispenser contains Lubri Gel for internal examinations, supplied as a service to medicine by Rhone-Poulenc Rorer Ltd". The Panel noted the supplementary information to Clause 18.2 that names of medicines should not be used on promotional aids when it would be inappropriate to do so. For example, when it might mislead as to the nature of the item. The Panel considered that the dispenser was adequately labelled. It did not accept that the use of the name, "Menorest", on the dispenser would mislead as to the nature of the item due to the explanation that followed. Neither did it accept the allegation that it might be assumed that the name of the product was Menorest Lubri Gel. Menorest was a transdermal patch for hormone replacement therapy and,

in the Panel's view, there could be no confusion. The Panel therefore ruled no breach of Clause 18.2 of the Code.

During its consideration of this case, the Panel noted that the dispenser was not labelled with the constituents of Lubri Gel. It considered that this would have been helpful but it was not a matter that came within the Code. The Panel also considered that medical information departments in companies should be informed in advance of the use of promotional aids, such as the item in question, so that they were able to answer enquiries. Rhone-Poulenc Rorer had not addressed this point in its response and the Panel noted that it appeared that the complainant had not received any response to her enquiries.

**Complaint received** 29 April 1996

**Case completed** 5 June 1996

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**Case AUTH/426/5/96** *NO BREACH OF THE CODE*

# ENT CONSULTANT v ALLEN & HANBURYS

## "Dear Doctor" letter on Flixonase and Beconase

**An ENT consultant complained about a letter from Allen & Hanburys which referred to the discontinuance of Beconase Nasal Spray, alleging that it was misleading because it gave the impression that all forms of Beconase would be discontinued and that only Flixonase would be available. Beconase Aqueous Nasal Spray would in fact remain available. The complainant commented that while a statement referring to cost savings when treating children with Flixonase compared to Beconase Aqueous Nasal Spray in the letter was true, Flixonase was more expensive than Beconase in adults.**

**The Panel considered that the letter could have been more explicit as to the Beconase Aqueous Nasal Spray remaining on the market but on balance did not consider it was misleading. The statement about the costs of usage in children was factual and the Panel did not consider it had any implication about the cost in adults. No breach of the Code was ruled.**

The material at issue was a "Dear Doctor" letter (ref HM3020 - CP/January 1996) sent by Allen & Hanburys Limited to all ENT consultants. The letter was headed "Countdown... Only two months until Beconase (beclomethasone dipropionate) Nasal Spray is discontinued" and it discussed the European Union ban on the manufacture of chlorofluorocarbons (CFCs). The letter stated that Beconase Nasal Spray was to be discontinued on 29 February 1996. A little further on the letter stated that the CFC free alternatives were Beconase Aqueous Nasal Spray and Flixonase Aqueous Nasal Spray. The letter then went on to talk about Flixonase in some detail. The letter was accompanied by a brochure on Flixonase (ref HM 3039 - CP/December 1995).

### COMPLAINT

A consultant complained directly to Allen & Hanburys alleging that the "Dear Doctor" letter was misleading. He was not alone in that his initial reading of the letter left him with the impression that all forms of Beconase were to be discontinued and that the only available preparation would be Flixonase. Whilst he accepted that on very careful reading of the letter it could be seen that the Beconase Aqueous Nasal Spray would still be available, the overall impression was that only Flixonase would be available.

The complainant further said that while it might be true that the treatment of children using Flixonase was marginally cheaper, for adults the use of Flixonase was considerably more expensive than treatment with Beconase Aqueous Nasal Spray. He had always used topical steroid preparations manufactured by Allen & Hanburys and had been satisfied with them. He was very disappointed by the advertising campaign. By persuading doctors to prescribe Flixonase instead of Beconase Aqueous Nasal Spray, Allen & Hanburys stood to gain financially in terms of the relative cost of the two preparations as well as the longer time run of the product licence for the new product.

The complainant had written to the author of the "Dear Doctor" letter but he had not received a reply.

### RESPONSE

Glaxo Wellcome said that it was sorry that any offence had been inadvertently caused to the complainant by the "Dear Doctor" letter in question. It could not agree that the letter was misleading by giving the impression that all forms of Beconase were to be discontinued. Beconase Nasal Spray was a trade name for the CFC aerosol form of Beconase. This was made clear in the second paragraph of the "Dear Doctor" letter. The alternative Beconase presentation was Beconase Aqueous Nasal Spray and this was made clear in paragraph five of the letter which clearly stated that the Allen & Hanburys CFC-free alternatives were either Beconase Aqueous Nasal Spray or Flixonase Aqueous Nasal Spray. The letter then offered a number of advantages to changing Beconase Nasal Spray patients to Flixonase Aqueous Nasal Spray after the discontinuation of Beconase Nasal Spray. These advantages, such as its indication for perennial rhinitis and hay fever in patients as young as four years of age, the negligible potential for systemic side effects from the swallowed portion of the intranasal dose and the once daily dosing regimen were not available from the CFC containing Beconase Nasal Spray and were reasonable comments.

The reference to Flixonase costs when used in children compared with Beconase Nasal Spray costs was factually correct. There was certainly no implication or suggestion

that the price differential applied when used in adults. The dosage information clearly differentiated between children aged four and over in whom one spray to each nostril in the morning could be used, and adults in whom two sprays in each nostril could be used. Equally, it was made plain that the pack containing 120 doses would last for thirty days in an adult and sixty days in children at standard daily doses.

Glaxo Wellcome was unhappy that the complainant had not received a reply but it appeared that his letter had not been received by the addressee. It had taken steps to address that situation and one of its medical advisers would be in contact with him.

## RULING

The Panel examined the "Dear Doctor" letter, which had been sent to all ENT consultants, and considered that it clearly amounted to a promotional item for Flixonase Aqueous Nasal Spray. That product featured predominantly in the "Dear Doctor" letter which referred also to Beconase Nasal Spray and Beconase Aqueous Nasal Spray and bore prescribing information for all three products. The letter was accompanied by a brochure on Flixonase.

There was nothing wrong with the letter being a promotional item for Flixonase. The question to be addressed was whether it had misled by its references to the discontinuation of Beconase Nasal Spray.

The Panel noted that the information to be gained from the heading to the letter and its first four paragraphs related to the discontinuation of Beconase Nasal Spray and the consideration of Flixonase as an alternative. It was not until one reached the fifth paragraph that one read that "The CFC-free alternatives from Allen & Hanburys are Beconase Aqueous Nasal Spray and Flixonase Aqueous Nasal Spray". The rest of the letter was largely concerned with the advantages of Flixonase but the final section dealt with the establishment of the Beconase Nasal Spray "Countdown Line" to deal with questions about the transition to CFC-free alternatives.

The Panel understood the reasons for the complainant's concern and considered that the "Dear Doctor" letter could have been more explicit as to the continuance on the market of Beconase Aqueous Nasal Spray. On balance, however, the Panel did not consider that the letter was misleading and ruled that there had been no breach of Clause 7.2 of the Code in that respect.

In relation to the complainant's criticisms of the reference to costs, the Panel noted that there was a postscript to the letter which stated "P.S. You may also be interested to know that Flixonase costs a penny a day less in children than Beconase Nasal Spray." The Panel considered that this was a claim which was in fact true. In the Panel's view it could not be taken to have any implication about the cost of usage in adults. The postscript was not misleading in this regard and the Panel therefore ruled no breach of Clause 7.2 of the Code.

**Complaint received** **2 May 1996**

**Case completed** **20 June 1996**

CASE AUTH/427/5/96

# E MERCK v SCHERING HEALTH CARE

## Progynova TS press release and journal advertisement

**Merck complained about a press release and a journal advertisement for Progynova TS issued by Schering Health Care. Merck alleged that as Progynova TS was launched onto the UK market later than the E Merck 7 day HRT patch, statements in the press release that Progynova TS was the only patch to deliver oestrogen over 7 days and the only one that needed to be changed every week were in breach of the Code. Merck alleged that the claim "The world's first 7-day HRT patch" in a journal advertisement was incorrect because Progynova TS was marketed in the UK and not globally. Merck also alleged a breach of Clause 2 of the Code given that the Panel had already ruled a breach of the Code in a previous case which related to a similar matter.**

**The Panel decided that the complaint about the press release had been covered by its previous ruling in Cases AUTH/395/2/96 and AUTH/405/2/96. The press release was issued before the material in question in the previous cases. The Panel's previous ruling was that it was misleading to claim that Progynova TS was the first seven day patch available in the UK given that the Merck product was the first seven day HRT patch available in the UK. With regard to the journal advertisement, the Panel considered that the claim as worded was true, the Schering Health Care patch was the first one in the world, and no breach of the Code was ruled. The Panel did not accept that the material was in breach of Clause 2 of the Code and no breach was ruled.**

E Merck Pharmaceuticals complained about the promotion of Progynova TS by Schering Health Care Limited. There were two complaints which were considered as follows:

### 1 Press release

The press release was dated 30 January 1996 and was headed "Neat, Petite and Very Discreet. The first 7-day HRT patch launched by Schering".

#### COMPLAINT

Merck provided a copy of the press release together with copies of articles about Progynova TS which had appeared in the media. Merck pointed out that the press release and the media articles stated that Progynova TS was the "only patch to deliver a continuous dose of oestrogen over seven days" and was "the only one that has to be changed every week". Progynova TS was launched on the UK market later than the E Merck seven day HRT patch, FemSeven, so clearly the statements were in breach of Clauses 2, 7.2, 7.3, 7.8, 20.1 and 20.2 of the Code.

#### RESPONSE

Schering Health Care Limited pointed out that the press release was issued on 29/30 January 1996 and was therefore part of its original launch campaign. It predated the complaint from Merck in Case AUTH/395/2/96 and was issued in good faith at a time when Schering considered that its product was the only seven day patch. A press release giving factual information about a new product was standard practice and did not constitute advertising to the general public. Thus the press release was not in breach of Clause 20 of the Code.

The company noted that the Panel had already ruled in Case AUTH/395/2/96 that some of the claims made were in breach of Clause 7.2 of the Code. The press release was based on an up-to-date evaluation of all the evidence in the company's possession at the time and to that extent it was not in breach of Clause 7.2. When the press release was issued the information was true and Merck did not appear to question the statements regarding the delivery of oestrogen or that the patch only needed to be changed once a week. The statements were not in breach of Clause 7.3. No exaggerated or all embracing claims had been made and it was therefore incorrect to allege a breach of Clause 7.8. The company denied that the material was in breach of Clause 2. It upheld the strictest standards checking all promotional material and press statements. Any claims made in connection with its launch campaign were made in good faith and in the light of the knowledge at that time.

Schering said that the Panel had already ruled that the advertisements at that time of launch were in breach of Clause 7.2. Although the company did not necessarily agree with the ruling it did of course abide by it and amended all its literature including press releases accordingly. The company strongly believed that it was being accused of the same breach of the Code twice and this complaint was therefore totally unjustified. It was the company's view that once the Panel had ruled on a complaint relating to a particular claim and that ruling had been accepted, the Panel should not deal with further complaints relating to the same claims contained in material which was issued not only before the Panel's ruling but before the original complaint was even submitted to the Authority.

#### RULING

The Panel examined the complaint and decided that the allegation related solely to the timing of the launch of the two seven day HRT products, Progynova TS and FemSeven. There was no complaint about the actual content of the press release. A number of breaches of the Code had been alleged but no details had been given. The Panel examined the press release and noted that it was dated 30 January 1996. The Panel noted that in Case AUTH/395/2/96, Merck had stated that its own seven day HRT patch, FemSeven, was available for prescription from 31 January. The Panel noted that Schering had stated in that case that it had understood that the Merck product was to be launched on 5 February 1996. The Panel had noted in its ruling that FemSeven had been available from wholesalers from 23 January 1996, Progynova TS from 5

February 1996 and that both products had been referred to as new products in the February edition of MIMS. The ABPI had received its copy on 2 February 1996.

Turning to the complaint now before it, the Panel noted that the press release had been issued on 29/30 January which was before the Merck product was launched. The Panel noted that at the time the press release was used by Schering Health Care it may not have been aware that Merck was to launch its product, FemSeven, the next day (31 January). Of course, following the launch of the Merck product, Schering would have known that its product was not the first seven day HRT patch.

The Panel noted that cases relating to articles in the media were judged on the information provided by the company or its agency to the media, as stated in the supplementary information to Clause 20.2 of the Code. The content of the published articles was not relevant in relation to whether or not there had been a breach of the Code.

The Panel considered that the heading to the press release "The first 7-day HRT patch launched by Schering" was ambiguous in that it could be taken to mean that this was the first seven day HRT patch to be launched by Schering and there could be others to follow from Schering, or it could be taken to mean that this was the first seven day HRT patch available in the UK. With regard to the dose of oestrogen, the press release said "Progynova TS will not only be the smallest patch on the market, but the only one to deliver a continuous dose of oestrogen (17b - oestradiol) over seven days, via the acrylate adhesive that holds the patch to the skin" and "Until now all other HRT patches have had to be changed every three to four days ... Progynova TS is simply changed on the same day of every week". These statements were not quite as given in Merck's complaint which had referred to the statements "only patch to deliver a continuous dose of oestrogen over seven days" and "the only one that has to be changed every week". It appeared that the statements quoted by Merck had been taken from the articles in the media rather than from the press release as such.

The Panel decided that the statement in the press release "The first 7-day HRT patch launched by Schering" could be taken to mean that Progynova TS was the first 7-day HRT patch in the UK. This view was supported by the content of some of the media articles. In the Panel's view the complaint related to the timing of the launch of the two products. The statements referred to by Merck were objected to because Progynova TS had been launched later than FemSeven. This had been addressed in the previous cases (AUTH/395/2/96 and AUTH/405/2/96), in which the Panel had decided that Merck's product FemSeven was the first 7-day HRT patch to be available in the UK. The Panel decided that the complaint now before it was covered by its previous ruling of a breach of Clause 7.2 of the Code in that it was misleading to claim that Progynova TS was the first 7-day HRT patch available in the UK.

## 2 Journal advertisement

### COMPLAINT

Merck provided two advertisements from the medical press which included the claim that Progynova was "The world's first 7-day HRT patch". Merck alleged that this was incorrect because Progynova TS was only marketed in the UK and not globally. Breaches of Clauses 7.2, 7.3, 7.8 and 20.2 were alleged.

### RESPONSE

Schering submitted that Progynova TS was the world's first seven day patch. It had been marketed in the USA as Climara since 8 May 1995. Progynova TS and Climara were the same patch. The company did not understand the alleged breach of Clause 20.2 as the advertisements were intended for medical practitioners only and not for dissemination to the general public.

### RULING

The Panel accepted the submission from Schering Health Care that Progynova TS was the world's first 7-day HRT patch. It noted that it had a different brand name in America but did not consider that this was relevant. The important point was that the patch itself was the first one in the world. Advertising to the public was not involved. The claim as worded was true and the Panel therefore ruled no breach of Code.

## 3 Alleged breach of Clause 2

### COMPLAINT

Merck alleged that the overall campaign, bearing in mind the findings of the Panel in the previous cases (AUTH/395/4/96 and AUTH/405/4/96), constituted a breach of Clause 2 of the Code.

### RESPONSE

Schering said that to imply that it had in any way contravened the previous rulings of the Authority was totally without foundation. At the completion of the previous cases, the materials were all withdrawn and changed to bring them in line with the rulings.

### RULING

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. It did not consider that the circumstances warranted a ruling of Clause 2 of the Code. No breach had been ruled in relation to the claim "The world's first 7-day HRT patch". Schering had amended its promotional material in the light of the Panel's rulings in Cases AUTH/395/2/96 and AUTH/405/2/96 and those rulings encompassed the matters relating to the press release. The Panel therefore ruled no breach of Clause 2 of the Code.

**Complaint received** **2 May 1996**

**Case completed** **18 June 1996**

CASE AUTH/428/5/96

# CONSULTANT PHYSICIAN v ALLEN & HANBURYS

## Flixotide mailing

**A consultant physician complained about a Flixotide mailing sent by Allen & Hanburys. The complainant alleged that the mailing was misleading as it compared Flixotide and Becotide and stated that the choice was clear. There was only limited comparative information supplied which was not sufficient to support the choice of Flixotide over Becotide.**

**The Panel considered that there was some evidence to support the mailing but it did not accept that there was sufficient to support the heading "The choice is clear" which was a strong claim. The mailing was ruled in breach of the Code as it was not balanced.**

The promotional item in question was a "Dear Doctor" letter on Flixotide (fluticasone) sent by Allen & Hanburys (ref HM 2944 - KP/Jan 1996). The letter was printed on a card with sections at the top and bottom that pulled out. The letter was headed "The choice is clear" and stated that "Flixotide represents an appropriate successor to Becotide". The two pull out sections printed on both sides compared Flixotide with beclomethasone dipropionate (Becotide). The mailing had been sent to target general practitioners and to hospital doctors (consultant to registrar grades) in general medicine, paediatrics and geriatrics.

### COMPLAINT

A consultant physician alleged that this unsolicited item contravened the Code, in particular Clause 7.2. The item implied that the choice was clear between fluticasone and beclomethasone but the comparative information provided related to the relative potency of the two drugs in a standard test of cortisosteroid potency, and in patients, and to a demonstration of changes in serum cortisol concentration after 4 weeks treatment with the two drugs which showed no significant adverse effects of either. None of the other statements regarding fluticasone was comparative.

The complainant said the statement "Considering that Flixotide is an extension of Allen & Hanburys' experience with Becotide, it is perhaps not surprising that Flixotide may have the potential to offer an improved efficacy to safety ratio compared to Becotide" was not only a *non sequitur* (the example of propranolol and practolol was cited) but none of the information provided was relevant to that statement.

The item implied that the information provided was relevant to deciding which of the two drugs to use in clinical practice. The complainant could not see anything in the comparative information which helped to make the claim or the choice.

### RESPONSE

Glaxo Wellcome submitted that the cited references fully supported the suggestion that Flixotide had a better efficacy to safety ratio than Becotide. Glaxo referred to three of the pages on the pull out sections of the card as follows:

### 1 Page headed "Flixotide: High topical anti-inflammatory activity"

The standard test of corticosteroid potency to which the complainant referred was the McKenzie test and Glaxo Wellcome agreed that this illustrated the approximately 2:1 potency difference, fluticasone propionate:beclomethasone dipropionate, which was apparent from preclinical screening.

The negligible oral systemic bioavailablility of fluticasone propionate was a matter of fact, but was relevant when considering the benefit:safety ratio. Beclomethasone dipropionate had such complex pharmacokinetics that no figures were presented in the referenced paper by Harding. The oral, systemic bioavailability for beclomethasone dipropionate was thought to be about 20% and the very low level for fluticasone propionate was relevant in that the swallowed fraction, up to 80% of the stated dose, might contribute to the systemic activity of an inhaled drug.

### 2 Page headed "Building on the experience of Becotide"

This section addressed improved asthma control in general terms, with reference to The Guidelines on the Management of Asthma issued by the British Thoracic Society. Below the heading appeared the statement "Improving asthma control may help patients to achieve the aims of asthma management" followed by three points. Glaxo Wellcome submitted that the first point, "to restore normal or best possible long term airway function", was supported by reference 11 (Fabbri *et al*), which studied a group of moderate to severe asthmatics treated with fluticasone propionate or beclomethasone dipropionate in doses of 1500 micrograms daily. There was a significant benefit for those patients on fluticasone propionate in terms of primary outcome measures, such as morning PEFR (peak expiratory flow rate), over the initial 3 month study period and the extension to 12 months.

The second point, "to reduce risk of severe attacks", was supported again by reference 11 as there was a significant reduction in severe exacerbations in the fluticasone propionate group.

### 3 Page headed "Flixotide. Effect on serum cortisol compared with Becotide"

The bar chart taken from the data presented in reference 8 (Dahl *et al*) showed a tendency towards a dose related reduction in mean morning serum cortisol for patients on increasing doses of an inhaled corticosteroid. However, when daily doses of fluticasone propionate which might be clinically equivalent to (200 micrograms) or be more efficacious (800 micrograms) than beclomethasone diproprionate 400 micrograms, were examined, the mean serum cortisols were not significantly different. At doses

which might be expected to be twice or four times as potent as 400 micrograms of beclomethasone dipropionate, the mean serum cortisols were within normal limits and were not statistically significantly different.

The company said that while the copy might not be explicit, the studies described in reference 10 (Barnes *et al*) and 11 (Fabbri *et al*) both supported the suggestion of an improved efficacy to safety ratio for fluticasone propionate compared to beclomethasone dipropionate. For example, reference 10 compared fluticasone propionate at doses of 1000 micrograms daily with beclomethasone dipropionate at 2000 micrograms daily. Outcome measures were comparable but mean serum cortisols were significantly in favour of fluticasone proprionate. As stated above, reference 11 studied patients using the same doses of fluticasone propionate and beclomethasone dipropionate, i.e. 1500 micrograms daily, and showed improved efficacy without any greater effect upon the hypothalamopituitary-adrenal axis, as measured by morning serum cortisol.

Glaxo Wellcome said that while some of the wording might have been clearer when related to the title line, it submitted that it was not necessary to reference every statement. It considered that the references quoted in the item did support the position that fluticasone propionate did have a more favourable efficacy to safety ratio than beclomethasone dipropionate and that this information might help the prescribing doctor when making decisions regarding choice of an inhaled corticosteroid in different stituations.

**RULING**

The Panel noted that it appeared that the dose of beclomethasone in reference 10 (Barnes *et al*) and reference 11 (Fabbri *et al*) was more than the maximum dose given in the prescribing information on the item in question. It further noted that reference 11 (Fabbri *et al*) used the same doses of the two products (1500 micrograms) although it was acknowledged that there was a 2:1 potency ratio between the products.

The Panel noted that the letter was headed "The choice is clear" with a subheading "Evolution in Practice". The letter stated, *inter alia*, "Specifically designed as an advance in steroid therapy, Flixotide represents an appropriate successor to Becotide" and "Considering that Flixotide is an extension of Allen & Hanburys' experience with Becotide, it is perhaps not surprising that Flixotide may have the potential to offer an improved efficacy to safety ratio compared to Becotide".

The Panel considered that there was some evidence to support the statement that Flixotide might have the potential to offer an improved efficacy to safety ratio compared to Becotide as stated in the text of the "Dear Doctor" letter. It did not accept that the available evidence was sufficient to support the heading to the letter, "The choice is clear", which was a strong claim. The Panel considered that the item was not balanced and therefore ruled a breach of Clause 7.2 of the Code.

**Complaint recevied** **7 May 1996**

**Case completed** **1 July 1996**

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**Case AUTH/429/5/96**

# PHARMACEUTICAL ADVISER v ASTA MEDICA

## Sponsorship of hay fever protocol

**A senior pharmaceutical adviser complained about the apparent involvement of Asta Medica in the circulation of a letter and a hay fever management protocol which had been sent to local general practitioners by an ENT consultant. The company's name was not given in the material and the complainant queried whether the protocol was entirely objective.**

**The Panel considered that the fact that Asta Medica had arranged for the production and circulation of the letter and protocol meant that it had sponsored them and a breach of the Code was ruled because of the failure to reveal that fact.**

This case related to a hay fever protocol which set out a number of treatment options. It had been accompanied by a letter from an ENT consultant and sent to local general practitioners. Asta Medica Limited, the company involved in the distribution of the documents, was not a member of the ABPI but had nonetheless agreed to comply with the Code.

**COMPLAINT**

A senior pharmaceutical adviser to a health authority sent the Authority a copy of the letter he had sent to Asta Medica about a letter and a hay fever management protocol which had been sent to local general practitioners by a consultant ENT surgeon. The complainant had himself received a complaint from a local GP who pointed out that the protocol contradicted previous advice issued by the health authority and that to use Rhinolast (an Asta Medica product) in the manner suggested would lead to a significant increase in prescribing costs.

The complainant said that at first glance the hay fever management protocol and its accompanying letter appeared to be an independent initiative by the consultant and the casual reader could be forgiven for assuming that they were endorsed by the local hospital trusts. However, the prominence given to Rhinolast suggested that the protocol was not entirely objective and the complainant had heard from another source that Asta Medica was involved in its production. If this was the case, the complainant was concerned that the company involvement was not apparent anywhere on the material.

Neither of the local trusts had approved Rhinolast at its Drug & Therapeutic Committee and the British National

Formulary and the Medicines Resource Centre regarded it as less effective than nasal steroids. The complainant had asked the company for information as to its involvement in the drawing up of the treatment choices included in the hay fever protocol, the printing of the protocol and its covering letter, and their distribution to GPs. He was also interested to know whether any financial inducements were received by the consultant in return for endorsing the guidelines.

### RESPONSE

Asta Medica Limited said that the hay fever protocol was not a document prepared or sponsored by it. It reflected the consultant's view of the choice of treatments available. Asta Medica sales representatives had indeed held discussions with the consultant on the management of hay fever and the use of treatment protocols as this was an area in which the consultant had expressed an interest during previous visits. The company assisted the consultant by making him aware of some of the protocols already in existence, although outside his referral area. Asta Medica understood that the consultant used the protocol of another ENT surgeon as the basis for his own version making changes and adjustments as he thought necessary.

Due to a shortage of resources within the consultant's department, Asta Medica had been pleased to respond to a request to assist with the printing and mailing of the hay fever protocol and covering letter which were originated and signed by the consultant. At no time in any of its discussions with the consultant was any financial inducement offered or taken.

Asta said that the inclusion of Rhinolast and the way in which it was described within the protocol was the consultant's decision at a time when Rhinolast was the only intra-nasal antihistamine spray available. The brand names of all other major nasal sprays for the treatment of hay fever were also included in the protocol.

### RULING

The Panel considered that the fact that Asta Medica had arranged for the printing and mailing of the letter and the protocol meant that Asta Medica had sponsored them and that fact had not been mentioned on either of the items. The Panel accordingly ruled that there had been a breach of Clause 9.9 of the Code.

As the Panel had ruled that the support given by Asta Medica to the circulation of the documents had been in breach of the Code, the Panel did not consider whether the protocol was an objective appraisal of the therapeutic area. It requested that the company be advised that if it was not objective then it might well be regarded as promotional material which would mean that other requirements of the Code had not been met.

**Complaint received** **7 May 1996**

**Case completed** **13 June 1996**

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**CASE AUTH/430/5/96** *NO BREACH OF THE CODE*

# PHARMACEUTICAL ADVISER v CIBA

## Estraderm/Estraderm MX exchange scheme

**A pharmaceutical adviser complained about Ciba's Estraderm/Estraderm MX exchange scheme alleging that it promoted a product directly to the public and bypassed the normal routes of dispensing.**

**The Panel noted that none of the materials had been sent or supplied to patients by the company either directly or via the doctor. The Panel did not consider that the scheme was unacceptable. No breach of the Code was ruled.**

### COMPLAINT

A pharmaceutical adviser complained about information sent by Ciba Pharmaceuticals concerning its Estraderm/Estraderm MX exchange scheme. The complainant queried whether the scheme was allowable under the Code. In the complainant's view the scheme could be considered as promoting a product directly to the public and, in addition, it bypassed the normal routes of dispensing and thus the associated safeguards.

### RESPONSE

Ciba Pharmaceuticals explained in detail its customer care Estraderm/Estraderm MX patch exchange scheme. The scheme was only available via general practitioners. If the general practitioner had a patient using Estraderm or Estraderm MX and for any reason it did not suit them, then the company would exchange the pack for the equivalent number of packs of the alternative up to a maximum of three months supply.

The company provided copies of mailings and information sent to general practitioners and medical and pharmaceutical advisers giving details about the scheme. To participate the general practitioner had to contact the Ciba Customer Care Department where the general practitioner's details and GMC number were taken by Ciba. The doctor then had to give reasons for the return and the number of packs returned. Ciba then sent the general practitioner replacement packs, a reply paid envelope for return of unwanted patches and a returned product coupon. The general practitioner filled in the form and returned it to Ciba with the unused patches. The general practitioner would then contact the patient and issue the new packs. The general practitioner was asked to contact the retail pharmacist and advise of changes to the patient's prescription.

Ciba pointed out that members of the public had no way of knowing about the scheme other than through the

general practitioner and then only after having been prescribed one of Ciba's HRT products which had been found not to be satisfactory. No statement was made to encourage any member of the public to ask their doctors to prescribe a specific medicine. The company's field force did not currently promote the exchange scheme. As Estraderm and Estraderm MX were bioequivalent and offered the same clinical benefits, the objective of the scheme was to allow patients to be maintained on a treatment with which they were already familiar and trusted and to receive the benefits of a more appropriate formulation without incremental cost to the NHS. The scheme had to be initiated by the general practitioner. No other person was involved and this could be regarded as parallel to the situation where dispensing doctors were able to provide patients with medicine without the intervention of a pharmacist. Furthermore, the prescription must have been initially written for the alternative product before the patient could take part in the scheme. The company did not believe the scheme could be interpreted as providing a sample.

**RULING**

The Panel noted that the exchange scheme related to the use of two of Ciba's products. A maximum of three months treatment could be exchanged. It was the general practitioner who initiated the scheme. The only way that patients would find out about the scheme would be from their doctors. The company had not communicated any of the details of the scheme to patients or the public. The Panel ruled that there was no breach of Clause 20 of the Code as none of the materials had been sent or supplied to patients by the company either directly or via the doctor.

The Panel noted the requirements of Clause 9.1 of the Code that all material and activities must recognise the special nature of medicines and the professional standing of the audience and must not be likely to cause offence and that high standards must be maintained. The Panel did not consider that the scheme was unacceptable and therefore ruled no breach of Clause 9.1 of the Code.

**Complaint received** **13 May 1996**

**Case completed** **11 June 1996**

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**CASE AUTH/431/5/96**

# ALCON v CIBAVISION

## Unacceptable promotional competition

**Alcon Laboratories alleged that a leaflet giving details of a competition was unacceptable as it included a question about CibaVision's medicine Iocare for which no prescribing information had been provided and the two prizes offered were excessive.**

**The Panel noted that the leaflet promoted a device, Ophthalin, but one of the competition questions showed a pack shot of Iocare a medicine, with the product name clearly visible. The question amounted to the promotion of Iocare and this meant that the leaflet as a whole, including the competition, was subject to the Code. A breach of the Code was ruled as prescribing information had not been given. The two prizes of travel and registration bursaries to attend an American Ophthalmology meeting in Chicago were ruled in breach as the cost would exceed that permitted in a promotional competition of £100 plus VAT.**

Alcon Laboratories (UK) Limited, a company not in membership of the ABPI, complained about a competition organised by CibaVision Ophthalmics. Details of the competition were given on a leaflet which included promotion of Ophthalin together with the prescribing information for that product. It had been mailed to all UK ophthalmologists. The competition prizes were two travel and registration bursaries to attend the American Academy of Ophthalmology meeting in Chicago in October 1996. The competition consisted of five questions. The fifth question was "What are the chemical constituents of this CibaVision Ophthalmics product?" and was located next to a pack shot of Iocare 500ml.

**COMPLAINT**

Alcon alleged that although Ophthalin, as a CE marked product, was outside the scope of the Code, Iocare was not. As no prescribing information for Iocare was included on the leaflet, a breach of Clause 4.1 was alleged. In addition Alcon alleged that the competition was in breach of Clause 18.2 especially with regard to the size of the financial prize offered.

**RESPONSE**

CibaVision submitted that as Ophthalin was classified as a medical device and was CE marked the promotional item was outside the scope of the Code.

CibaVision acknowledged that a pack shot of Iocare appeared in the leaflet as part of one of the competition questions. Iocare Balanced Salt Solution was a licensed medicinal product. However, the item was not intended as promotion of Iocare.

CibaVision submitted that the leaflet was not promotional as the mention of Iocare was very low key, no claims were being made for the product, the question being asked was within the context of the rest of the competition, the text itself did not mention the Iocare name at all, the pack shot was very small in relation to the size of the whole leaflet and particularly in relation to the size of the Ophthalin advertisement.

### RULING

The Panel noted that promotional items for Ophthalin would fall outside the scope of the Code as Ophthalin was a medical device and not a medicine. The Code only applied to the promotion of medicines. Clause 1.3 defined a medicine as any branded or unbranded medicine intended for use in humans which required a marketing authorization. The Panel noted that Iocare was a medicine and therefore the promotion of Iocare was subject to the Code.

It was a well established principle that the mention of a product name in advertising meant that the advertisement needed to comply with the Code and therefore prescribing information for the product mentioned was required. The Panel noted that the name for Iocare was clearly visible from the pack shot in the leaflet and this meant that the item as a whole, including the competition was subject to the Code.

The Panel considered that the reason that the question "What are the chemical constituents of this CibaVision product?" had been included was to draw attention to Iocare and therefore promote it. In order to answer the question it would be necessary for some doctors at least to refer to the data sheet or another source. No prescribing information for Iocare had been included in the piece. The Panel therefore ruled a breach of Clause 4.1 of the Code.

The Panel noted that competitions were not an unacceptable form of promotion provided that certain conditions were met and these were given in the supplementary information to Clause 18.2. The maximum acceptable cost to the donor of a prize in a promotional competition was £100 plus VAT and the number of prizes must be limited. There were two prizes offered in the competition in question. Both were travel and registration bursaries to attend the American Academy of Ophthalmology meeting in Chicago in October 1996. In the Panel's view the cost to CibaVision of each of these prizes would exceed £100. The Panel ruled a breach of Clause 18.1 of the Code.

**Complaint received** **17 May 1996**

**Case completed** **2 July 1996**

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**CASE AUTH/432/5/96**

# RHONE-POULENC RORER v CIBAVISION

## Livostin journal advertisement

**Rhone-Poulenc Rorer alleged that a journal advertisement for Livostin Eye Drops and Livostin Nasal Spray, issued by CibaVision, was misleading. A claim that Livostin did not cause irritation was at variance with the prescribing information which listed local irritation as a possible adverse reaction.**

**The Panel ruled that the claim was misleading as it was inconsistent with both the prescribing information and the data sheets for the products.**

### COMPLAINT

Rhone-Poulenc Rorer Limited complained about the promotion of Livostin by CibaVision Ophthalmics. The material at issue was a journal advertisement (ref no: CVO 283) which appeared in Doctor, 4 April 1996. Rhone-Poulenc Rorer pointed out that the advertisement claimed that Livostin did not cause irritation and alleged that this was at variance with the prescribing information for the product which cited local irritation as a specific adverse reaction. A breach of Clause 7.2 of the Code was alleged.

### RESPONSE

CibaVision pointed out that the claim in the advertisement was "Livostin works where it's needed - in ocular and nasal mucosa - without causing irritation" and acknowledged that the prescribing information did list local irritation as a possibile side effect. The claim was based on the reference cited (Janssens and Vanden Bussche) which stated "and it is not irritating to the nasal or ocular mucosa". Further review of the literature also supported the claim showing that the incidence of irritation with Livostin was generally low and was similar to that found with placebo.

CibaVision said that the prescribing information gave irritation as a potential side effect because there had been some reports of local irritation. With topically applied products there would always be a certain incidence of local irritation. Also, local irritation was part of the symptomatology of the condition being treated which made the assessment of the incidence of this effect difficult.

CibaVision concluded that the incidence of local irritation was generally low but that it was a possible side effect.

### RULING

The Panel noted that the prescribing information given in the advertisement was for both Livostin Eye Drops and Livostin Nasal Spray. Local irritation was listed as an adverse reaction common to both products.

The Panel noted that CibaVision submitted that the claim in question was based on a published paper and there was further support in the literature for the claim that the incidence of irritation caused by Livostin was low.

The Panel considered that it was misleading to claim in the advertisement that Livostin did not cause irritation when the prescribing information gave local irritation as an adverse reaction and local irritation appeared under

the heading "side effects" in the data sheets for the products. A breach of Clause 7.2 of the Code was ruled. Claims made for a product must not be inconsistent with the summary of product characteristics or data sheet.

**Complaint received** **17 May 1996**

**Case completed** **2 July 1996**

## CODE OF PRACTICE REVIEW - AUGUST 1996

Cases in which a breach of the Code was ruled are indexed in **bold** type.

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|---|---|---|---|---|
| **387/1/96** | **GP v Ciba** | **Promotion of Foradil & conduct of representatives** | **Breach 7.4** | **No appeal** |
| **394/2/96**<br>**407/3/96** | **Glaxo Wellcome & GP v Ciba** | **Promotion of Foradil** | **Breach 3.2 & 7.2** | **No appeal** |
| 398/2/96 | Glaxo Wellcome v Lilly | Axid advertisement | No Breach | Appeal by complainant |
| **399/2/96** | **GP v Wyeth** | **Article in company newsletter** | **Breach 7.2** | **No appeal** |
| **401/2/96** | **Leo v E Merck** | **Curatoderm press release** | **Breach 7.2 & 7.7** | **No appeal** |
| **404/2/96** | **Leo v E Merck** | **Curatoderm promotional item** | **Breach 7.2** | **Appeal by complainant** |
| 406/2/96 | University doctor v Hoechst Marion Roussel | Tarivid 400 mailing | No Breach | Appeal by complainant |
| **409/3/96** | **Ethics Committee Chairman v Servier** | **Cardiovascular risk evaluation** | **Breach 10.2 & 18.1** | **No appeal** |
| **410/3/96** | **E Merck v Leo** | **Dovonex press materials & "Dear Doctor" letter** | **Breach 7.2** | **No appeal** |
| **412/3/96** | **Schwarz v Bayer** | **Cost comparison chart in Adalat advertisement** | **Breach 7.2** | **No appeal** |
| **414/3/96** | **GP v Bristol-Myers Squibb** | **Dutonin advertisement** | **Breach 7.6** | **No appeal** |
| **418/3/96** | **Wyeth v Novo Nordisk** | **Kliofem mailing** | **Breach 7.2 & 7.3** | **No appeal** |
| **420/4/96**<br>**422/4/96** | **Director/Scrutiny & Medicines Control Agency v Norton Healthcare** | **Advertisements for an inhaler** | **Breach 4.1** | **No appeal** |
| 423/4/96 | Medicines Control Agency v Procter & Gamble | "Dear Doctor" letter on Didronel PMO. | No breach | No appeal |
| 424/5/96 | Hospital Pharmacist v Rhone-Poulenc Rorer | Menorest promotional aid | No breach | No appeal |
| 426/5/96 | ENT Consultant v Allen & Hanburys | "Dear Doctor" letter on Flixonase & Beconase | No breach | No appeal |
| **427/5/96** | **E Merck v Schering Healthcare** | **Progynova TS press release & journal advertisement** | **Covered by breach ruling in previous case** | **No appeal** |
| **428/5/96** | **Consultant Physician v Allen & Hanburys** | **Flixotide mailing** | **Breach 7.2** | **No appeal** |
| **429/5/96** | **Pharmaceutical Adviser v Asta Medica** | **Hay fever management protocol** | **Breach 9.9** | **No appeal** |
| 430/5/96 | Pharmaceutical Adviser v Ciba | Estraderm/Estraderm MX exchange scheme | No breach | No appeal |
| **431/5/96** | **Alcon v CibaVision** | **Promotional competition** | **Breach 4.1 and 18.1** | **No appeal** |
| **432/5/96** | **Rhone-Poulenc Rorer v CibaVision** | **Livostin advertisement** | **Breach 7.2** | **No appeal** |

# 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 for promotional purposes
- the sponsorship of promotional meetings
- the sponsorship of scientific 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 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).