PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

# CODE OF PRACTICE REVIEW

NUMBER 22 NOVEMBER 1998

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.

# The Internet

**The International Federation of Pharmaceutical Manufacturers Associations (IFPMA) held a symposium on the Internet in October and has now issued the position paper on "The use of the Internet for pharmaceutical information" which is reproduced below. The Authority issued guidance on the Internet and the Code of Practice in May 1996 and copies of that guidance are available upon request.**

### THE IFPMA POSITION

The Internet has the potential to be a vital and positive resource for society. Although it is continuing to evolve, it has already demonstrated its remarkable ability to inform and educate global audiences on a wide range of subjects including healthcare and medicinal products.

- The research-based pharmaceutical industry, represented by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), strongly supports the right to use the Internet as a means for providing accurate and scientifically reliable information on medicines in a responsible manner, for the benefit of both patients and healthcare professionals.

- Measures to regulate the Internet require caution as they could inadvertently impose unacceptable constraints on legitimate communication and information activities. The unscrupulous will always evade controls whilst the law-abiding will comply. Inappropriate regulation could result in a situation where unregulated and unreliable sources of information remain available on the Internet, unchallenged by reliable, authentic sources and legal authorities.

### REGULATION AND SELF-REGULATION

- The pharmaceutical industry has a long tradition and experience of self-regulation, self-auditing and the implementation of codes of Good Practice, including codes governing marketing and promotional practices. IFPMA is convinced that self-regulation is the method of choice for controlling the type and quality of information provided by pharmaceutical companies via the Internet, on pharmaceutical products.

- Wherever they market their products, world-wide, pharmaceutical companies within the membership of IFPMA are bound by the self-regulatory IFPMA Code of Pharmaceutical Marketing Practices. The Code sets out principles and standards for the information provided by companies about their products, and these requirements are equally valid for and applicable to information made available via the Internet.

*Continued overleaf column 1*

# Offers on reply paid cards

Two complaints dealt with by the Authority recently have related to reply paid cards which offered items to doctors which would be delivered by representatives. Case AUTH/646/11/97 in the May issue of the Review and Cases AUTH/695/4/98 and AUTH/696/4/98 in this issue refer. Breaches of Clause 15.3 of the Code were ruled in each case following appeals by the companies concerned.

The view of the Code of Practice Appeal Board is that reply paid cards which refer to representatives delivering items should either offer an alternative delivery option or explain that there is no obligation to grant the representative an interview when the item is delivered. This is to avoid the impression given by many such cards that there is such an obligation, which would be contrary to Clause 15.3 which prohibits the use of any inducement to gain an interview.

### SALE AND SUPPLY VIA THE INTERNET

- IFPMA shares concerns that the Internet can be misused by the unscrupulous, as a means to by-pass normal controls and to sell prescription medicines directly to patients, without appropriate professional consultation. Patients' health may be put at risk by such practices and industry supports measures to prevent such activities and to educate consumers about the dangers of procuring medicines in this way.

- Other forms of commerce involving the sale and supply of medicines via the Internet may also result in medicines being handled outside regulated distribution channels, with the danger that poor quality products, unlicensed medicines and counterfeits will be supplied.

- The nature of the Internet makes it difficult to enforce effective controls over those who misuse the Internet to advertise illicit services. Regulation and enforcement activities by legislative bodies or by government should, therefore, focus on the physical movement of goods via brokers, agents and dealers who are handling medicines and distributing them outside legitimate, authorised channels.

- The pharmaceutical industry recognises its responsibilities to ensure that its own products are only provided through legitimate and reputable channels. Industry has and will continue to work cooperatively with governments, regulatory bodies, and customs agencies to prevent the sale of medical products outside lawful distribution channels.

### FUTURE CHALLENGES

IFPMA, its member associations, and pharmaceutical companies, recognise the healthcare challenges presented by the global dimensions of the information available on the Internet but believe that these should be regarded as an opportunity for constructive changes, with the interests of the patient as the priority.

- Patients and consumers are seeking more information about medicines and medical treatment but laws and regulations differ widely throughout the world, with regard to the information which may be provided by companies on the products that they supply.

- Similarly, patients in remote areas, the elderly and incapacitated are seeking better access to medicines but there are major differences in the acceptability of "distance selling", even with appropriate safeguards for prescription controls.

Laws, regulations and medical culture differ in different parts of the world and the evolution of the Internet has brought the need for greater harmonisation into sharp focus. Greater uniformity in the international norms for disseminating accurate and reliable information on the use and availability of pharmaceutical products would make implementation and enforcement a much more tangible goal to the benefit of the patient and healthcare professionals in all regions.

## Advertising to health service managers

The Code permits the promotion of prescription medicines to health service administrative staff but Clause 12 of the Code states that "Promotional material should only be sent or distributed to those categories of persons whose need for, or interest in, the particular information can reasonably by assumed".

This means that promotional material sent to health service managers and the like must be relevant to their work. Material prepared for clinicians may or may not also be appropriate for managers. More targeted material may be needed.

A number of cases reported in this issue of the Review (AUTH/720/6/98, AUTH/729/6/98, AUTH/730/6/98, AUTH/737/7/98, AUTH/738/7/98 and AUTH/743/7/98) focus on this distinction.

## Meetings attended by patients

Companies are reminded that if they exhibit at meetings and conferences at which patients will be present, such as those involving patient groups, then the materials on their stands must be appropriate for the general public. That is to say that there must be no promotion of prescription only medicines to patients.

In a case reported in this issue of the Review (AUTH/742/7/98) it was alleged, though not supported by adequate evidence, that a patient had been given a sample of a prescription only medicine at such a meeting.

## New member of the Authority's staff

The Authority has welcomed Miss Bridget Carmody to its staff. Bridget is the Secretary to Etta Logan and Jane Landles. Her telephone number is 0171 930 9677 extension 1473.

# CODE OF PRACTICE TRAINING

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

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

Forthcoming Code of Practice seminar dates are:
Thursday, 11 February 1999,
Friday, 12 March 1999.

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 Vicki Meyrick for details (0171-930 9677 extn 1443).***

**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 Vicki Meyrick (0171-930 9677 extn 1443).

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

Heather Simmonds: 0171-747 1438
Etta Logan: 0171-747 1405
Jane Landles: 0171-747 1415

The above are available to give informal advice on the application of the Code of Practice.

The Authority rather than the ABPI is the contact point for information on the application of the Code.

CASE AUTH/677/2/98

# WYETH v ASTRA

## Losec detail aid

Wyeth made a number of allegations about a detail aid, issued by Astra, which compared Losec (omeprazole) with Wyeth's product Zoton (lansoprazole). Astra appealed a number of the Panel's rulings to the Appeal Board.

The referencing format was alleged to be misleading. Wyeth stated that the papers referred to in the detail aid had had their titles changed by Astra, and were not those used in the papers themselves. The Panel noted that each reference had been provided by listing the author, journal, year, volume and page number thus ensuring that they could be located as required by the Code. Each reference was followed by a brief description of the study. The Panel did not think that the descriptions would be taken to be the titles given their style and length. No breach of the Code was ruled.

Wyeth alleged that a page headed "Losec can provide greater acid suppression than lansoprazole" was not a balanced review of the evidence. Data from the referenced study showing that lansoprazole 15mg was equipotent to omeprazole 20mg and that lansoprazole 60mg was equipotent to omeprazole 40mg had been omitted from the bar charts. Other data was available which did not appear to have been considered by Astra, one of which directly contradicted information provided by it. The studies were in healthy volunteers but the only mention of this was in the reference at the bottom of the page. In the Panel's view, the bar charts gave the impression that there was no dose of lansoprazole which was equivalent, in terms of raising gastric pH, to the most effective dose of Losec, 40mg, which was not the case. The bar charts were misleading and a breach of the Code was ruled. This was upheld on appeal. A breach was also ruled as the heading was misleading. This was upheld on appeal as most readers would interpret it to mean that Losec always provided greater acid suppression. The word "can" was not enough to qualify the claim. The Panel considered that in terms of other data the study used was not unrepresentative and no breach was ruled in that regard. A breach was ruled because it had not been made sufficiently clear that the data related to healthy volunteers. This was also upheld on appeal.

Wyeth alleged that a page headed "Losec 40mg daily can provide greater acid suppression than lansoprazole 60mg daily" implied that Losec 40mg was more potent than lansoprazole 60mg and the evidence did not support this. The statement "At high daily doses licensed for *H. pylori* eradication" and the bar charts suggested that for *H. pylori* eradication Losec 40mg was a better choice than lansoprazole 60mg. The data portrayed was misleading. Successful *H. pylori* eradication required a pH greater than 5 but the referenced data reported on pH levels greater than pH 3 or 4. Wyeth had the same allegation as previously about the positioning of the statement on healthy volunteers. The Panel did not accept Astra's contention that the claim in the heading was qualified by the word "can". Readers would interpret it as meaning that it would happen always. A breach of the Code was ruled. This was upheld on appeal. In relation to the bar charts, the Panel considered that the use of the study upon which they were based, which had been carried out on *H. pylori* negative controls, under the statement "At high daily doses licensed for *H. pylori* eradication" was confusing given Astra's submission that *H. pylori* status was known to affect gastric acid suppression. The data did not reflect the balance of the evidence and a breach was ruled. The previous ruling concerning healthy volunteers also applied here.

Wyeth alleged that a page headed "Increasing acid suppression increases clinical response" was in breach because the data presented focussed on the healing of duodenal ulcers. The recognised cornerstone of successful duodenal ulcer treatment was the eradication of *H. pylori*, not the use of 4 weeks' acid suppression. To suggest otherwise was inaccurate and misleading. The Panel noted that the preceding pages of the detail aid had concentrated on the acid suppression achieved with Losec 40mg. The page in question presented the clinical response that might be achieved, ie the healing of duodenal ulcers. In the Panel's view it was acceptable to present such data. Although the importance of *H. pylori* eradication was not mentioned on the page in question, the audience would be aware of it. No breach of the Code was ruled.

In relation to a page headed "Lansoprazole does not offer dose-dependent healing", Wyeth stated that 30mg was the optimum dose of lansoprazole and to suggest otherwise was misleading. The data had been carefully selected to give the lowest 2 and 4 week healing rates and no mention was made of studies which did show dose dependent healing. Wyeth alleged that the selective use of data was disparaging and misleading. The Panel noted that the page featured a bar chart comparing the percentage of patients with a healed duodenal ulcer after 2 and 4 weeks' treatment with lansoprazole 30mg or 60mg. Above the bar chart was the statement "Lansoprazole 30mg is the only licensed dose for healing", which was in accordance with its data sheet. The Panel considered that the page was misleading as a 60mg dose was not relevant to the licensed indication and the bar chart depicted one of the lower healing rates reported with lansoprazole 30mg. A breach of the Code was ruled. In the Panel's view the heading "Lansoprazole does not offer dose dependent healing" implied that this was a disadvantage but 30mg, the dose licensed for the healing of duodenal ulcers, achieved rates comparable to Losec. The question of dose dependent healing appeared irrelevant. The Panel considered that the page disparaged lansoprazole and a breach was ruled. Upon appeal, the Appeal Board considered that the four week healing rates for Losec 20mg and 40mg and lansoprazole 30mg were comparable. That no greater healing rate was achieved using an unlicensed dose of lansoprazole was irrelevant. The Panel's rulings that the page was misleading and disparaging were upheld.

Wyeth alleged that a page headed "High acid suppression for high healing rates in duodenal ulcer" was in breach as the cornerstone of successful duodenal

ulcer treatment was eradication therapy rather than acid suppression alone. The Panel noted that the page in question examined the relationship between acid suppression and rates of duodenal ulcer healing with Losec, ranitidine and cimetidine. In the Panel's view it was acceptable to present such data. Although the importance of *H. pylori* eradication was not mentioned, the audience would be aware of it. No breach of the Code was ruled.

A page headed "*Helicobacter pylori* eradication in 7 days" presented data on the rates of *H. pylori* eradication of Losec in combination with various antibiotics. Wyeth alleged that the headline was all embracing but the Panel considered that given the therapy area and the audience, the headline would not be read to mean that Losec had a 100% success rate in 7 days and no breach was ruled. A claim below the headline said that Losec offered the combination of high acid suppression for healing duodenal ulcer with a range of antibiotics to effectively eradicate *H. pylori*. The Panel did not accept Wyeth's contention that this implied duodenal ulcer healing in 7 days. The 7 days was clearly limited only to *H. pylori* eradication. No breach of the Code was ruled. The Panel also ruled no breach in relation to an allegation that the data provided were not balanced and no breach in relation to an allegation that the dose of Losec used in a quoted study had been 20mg bd whereas in the detail aid the dose was given as 40mg/day. While it might have been helpful to have given the specific dosage, 40mg/day was not incorrect. Wyeth alleged that data on the page was misleading as the patient population in a quoted study had endoscopically confirmed duodenal ulcer, gastric ulcer or non-ulcer dyspepsia. However the triple therapy regimen referred to (OAM) was licensed for eradication in duodenal ulcer only and to report on patients with other *H. pylori* positive conditions was outside the licence terms. Further, the study was also single centre open. Given the recent focus on the credibility of *H. pylori* eradication studies and the requirement for them to be multi-centre, double-blind etc, the use of the study seemed to Wyeth to be inappropriate. Finally, no mention was made of which statistical analysis was presented. The Panel noted that the description of the study lacked any details regarding its design. It was a single centre open study. It would have been helpful to include such details but their omission did not mislead and no breach was ruled. Further, the Panel did not consider that the failure to specify which analysis had been used misled and no breach was ruled. The Panel considered that to quote a specific eradication rate that included patients other than those for which OAM therapy was indicated was misleading and a breach was ruled in that regard. Upon appeal of this ruling, the Appeal Board noted that triple therapy was not a licensed regimen for patients with gastric ulcers. The data included patients for whom the regimen used was unlicensed. In the Appeal Board's view, it was misleading to quote a specific eradication rate that included patients other than those for whom OAM was indicated and the Panel's ruling of a breach was upheld.

Wyeth stated that a heading "In a highly acid sensitive condition: erosive reflux oesophagitis" clearly indicated that the page dealt with erosive reflux oesophagitis as did the sub-heading which referred to complicated reflux oesophagitis and the graphical representation of study data. Only in the reference at the bottom of the page did it become apparent that the study actually dealt with the much rarer condition of reflux complicated by strictures. By implication any results would be potentially misleading. In the Panel's view all of the terms related to generally severe oesophagitis. The Panel did not consider that the use of the different terms was misleading and no breach was ruled. Wyeth stated that the implication of the bar chart was that only 20% of lansoprazole patients were likely to remain in remission, compared with 90% of Losec patients. This was in contrast to another study in which a similar population of patients received treatment with lansoprazole 30mg and 77% had no dysphagia at six months. The Panel did not consider that the 20% figure shown in the detail aid represented the balance of the evidence with regard to the efficacy of lansoprazole in oesophagitis and a breach was ruled. A breach was also ruled because the Panel considered that it was misleading not to have explained that there were two phases in the study in question, an initial 8 week healing phase when all patients received omeprazole, followed by a 4 week maintenance phase when patients were randomised to omeprazole, lansoprazole or pantoprazole. The Panel rejected an allegation that use of the data in question disparaged the medical profession because it was not representative of current medical practice. Upon appeal the Appeal Board accepted that the two studies were very different and their results could not be compared. The Appeal Board was concerned that a whole page of the detail aid and a major claim had been based on a scientific abstract reporting results in a small number of patients. The comparisons made in the study were not sufficiently qualified. The page was not balanced or fair and the Panel's ruling of a breach was upheld.

A breach was ruled by the Panel in relation to a misleading heading "Losec's efficacy in eradicating *H. pylori* makes it highly cost-efficient". It implied that Losec alone eradicated *H. pylori* which was not so. Astra successfully appealed this ruling. There were two bar charts and these gave a figure for Losec (OAM) of £21.71 cost per patient *H. pylori* eradicated and figures of £23.39 to £30.72 for lansoprazole with various licensed antibiotic combinations. Wyeth alleged that the representation of the data was misleading as the trials were not comparable. The Panel noted that the cost data for Losec had been calculated from a study in patients with duodenal ulcers, gastric ulcers and non-ulcer dyspepsia. OAM therapy was indicated as *H. pylori* eradication therapy only for patients with duodenal ulcers. The Panel considered that to base treatment costs on a specific eradication rate in patients other than those for whom OAM therapy was indicated was misleading and a breach was ruled. No breach was ruled in relation to an allegation about the lack of detail regarding the design of the study. The Panel considered that to include details would have been helpful but their omission did not mislead. Upon appeal of the ruling that the cost comparison was in breach, the Appeal Board considered that it was misleading to base the cost of therapy on a specific eradication rate reported in patients other than those for whom OAM therapy was indicated. Costs of the various triple therapies varied with the choice of antibiotics and to quote prices for some but not others had the effect of making lansoprazole based therapy appear more expensive than omeprazole based therapy. The Appeal Board considered that the cost data was misleading and upheld the Panel's ruling of a breach.

Wyeth alleged that a page headed "High patient tolerability" featuring two bar charts depicting the

**percentage of patients with adverse events was misleading. The Panel noted that the bar charts gave the percentage of patients with adverse events after 0-12 months as 38% and after 12-24 months' treatment with lansoprazole as 48.6% but this was not statistically different to the 34.5% reported for ranitidine. The impression given by the two bar charts was that the percentage of patients with adverse events on lansoprazole was more than with Losec. The Panel noted that there was other data available showing that the incidence of adverse events for lansoprazole and omeprazole was comparable. The Panel considered that the presentation of the data regarding patient tolerability did not represent the balance of the evidence and was misleading. A breach of the Code was ruled.**

Wyeth complained about a detail aid for Losec (omeprazole) (ref LOS/DAD 2036) issued by Astra Pharmaceuticals Ltd, making a number of specific allegations and claiming that the item was so misleading that it could potentially reduce confidence in the pharmaceutical industry as a whole. Wyeth also provided copies of leavepieces from the same campaign but made no specific allegations about these. Wyeth was the supplier of Zoton (lansoprazole).

Astra stated that the detail aid had been designed specifically for use in hospitals. Its format and layout were tested with hospital physicians and found to be acceptable to this type of audience prior to use by Astra's sales force. Other materials sent in by Wyeth had also been used in the hospital campaign.

### 1 Referencing format

#### COMPLAINT

Wyeth was concerned with the referencing format that had been followed throughout the detail aid. It appeared that the papers referred to throughout the detail aid had had their titles changed by Astra; the "titles" supplied were not those quoted on the papers themselves. That alone was misleading and was in breach of Clause 7.5.

#### RESPONSE

Astra referred to Clause 7.5 which stated that when promotional material referred to published studies, "clear references must be given". The referencing format employed stated clearly the location of the studies within the literature (journal, year, volume, page) and the author. The "titles" referred to had not been changed but were additional descriptions of methodology, expanding the range of information provided in the detail aid. The actual references had also not been changed. The study descriptions were added following feedback from Astra's market research with hospital physicians. Astra therefore rejected any breach of Clause 7.5.

#### PANEL RULING

The Panel noted that each reference had been provided by listing the author, journal, year, volume and page number thus ensuring that the papers could be located within the published literature as required by Clause 7.5 of the Code. Following each reference there was a brief description of the study. The Panel did not consider that, given the style and length of these descriptions, any of them would be taken to be the titles of the papers concerned. The Panel noted that when titles of papers were given these details usually appeared immediately after the authors' names and before the journal details and not at the end of the citation. No breach of the Code was ruled.

### 2 Heading "Losec can provide greater acid suppression than lansoprazole"

This page featured two bar charts showing acid suppression in terms of median 24 hour pH and percentage inhibition of 24 hour intragastric acidity. Each chart showed results for Losec (omeprazole) 20mg and 40mg and lansoprazole 30mg. Both bar charts showed that the favourable results for Losec 40mg were statistically significantly different to Losec 20mg and lansoprazole 30mg. The page was referenced to Seensalu *et al* (1995).

#### COMPLAINT

Wyeth alleged that this page was in breach of Clauses 7.2 and 7.6. The message being presented was not representative of either the referenced data or a balanced review of currently available data. Wyeth provided copies of six alternative studies examining the effect on gastric pH of lansoprazole and omeprazole (Dammann *et al* (1997); Janczewska *et al* (1997); Hedenström *et al* (1997); Bruley Des Varannes et al (1994); Tolman *et al* (1997) and Blum *et al* (1997)).

In the referenced study (Seensalu *et al* (1995)), lansoprazole 15mg, 30mg and 60mg versus omeprazole 20mg and 40mg were evaluated. In addition to the data depicted, the paper also showed that lansoprazole 15mg was equipotent to omeprazole 20mg, and lansoprazole 60mg was equipotent to the Losec 40mg. However the data relating to lansoprazole 15mg and 60mg had been omitted from the graph so breaching Clauses 7.2 and 7.6.

There was a wealth of data available with regard to acid suppression which did not appear to have been considered by Astra, one of which directly contradicted the information supplied by it. Astra's selective use of the data breached Clause 7.2.

All the above studies were in healthy volunteers. Whilst this was accepted as a suitable pharmacodynamic model, it was nevertheless not the same as intragastric pH measurement in patients, and Wyeth considered it ethical to ensure that this fact was emphasised. The only mention of this fact was in the "title" at the bottom of the page; it would seem more appropriate to have such a statement placed more centrally.

#### RESPONSE

Astra stated that the Seensalu study was a randomised, double-blind, five-way cross-over study, comparing the effects of lansoprazole 15, 30 and 60mg with omeprazole 20 and 40mg on intragastric acidity and gastric concentration profiles. Whilst Losec 40mg was statistically significantly superior to lansoprazole 30mg, Wyeth was right to point out that the results from the lansoprazole 60mg dosage had not been included. These did not show a significant difference between Losec 40mg

and lansoprazole 60mg, although the trend (87% inhibition versus 80%;ns) clearly favoured omeprazole 40mg and was consistent with the findings of the Geus *et al* (1997) study which were also depicted in the detail aid. The message presented did therefore reflect the referenced data.

Astra stated that these graphs were used in the Losec leavepiece (ref LOS LVP 2330) which had been the subject of recent correspondence between Wyeth and Astra. Astra had already agreed to make amendments to clarify the sections on the Geus and Seensalu data.

Regarding the concern expressed that the positioning of the study description in the title at the bottom of the page did not throw sufficient emphasis on the fact that this was a healthy volunteer study, it was made clear within the study description and stated specifically that the comparison was conducted in "16 healthy volunteers"; it did not therefore mislead. The lack of a "more central placement" did not therefore breach the Code. Furthermore, hospital physicians and Wyeth accepted that human volunteer studies were a suitable pharmacodynamic model in this case.

Astra rejected the allegations that breaches of Clauses 7.2 and 7.6 had occurred.

## PANEL RULING

The Panel noted that the Seensalu study had examined the effects on gastric pH of two doses of Losec, 20mg and 40mg, and three doses of lansoprazole, 15mg and 30mg and 60mg. The bar charts in question, while showing all the results for Losec, only gave the results for the 30mg dose of lansoprazole. The charts showed that in terms of median pH and inhibition of intragastric acidity over a 24 hour period, Losec 40mg was statistically significantly better than both Losec 20mg and lansoprazole 30mg. The Panel noted that if the results for the three doses of lansoprazole had been shown readers would have seen that there was no statistical difference between Losec 40mg and lansoprazole 60mg and nor between Losec 20mg and lansoprazole 15mg or 30mg.

In the Panel's view the bar charts gave the impression that there was no dose of lansoprazole which was equivalent, in terms of raising gastric pH, to the most effective dose of Losec, 40mg, which was not the case. The Panel considered that the bar charts were misleading in breach of Clause 7.6 of the Code. In addition the heading to the page, "Losec can provide greater acid suppression than lansoprazole" was misleading. The Panel ruled a breach of Clause 7.2.

The Panel noted that Astra had agreed to amend the claims based on the Seensalu data but no further details were given.

The Panel examined the six studies provided by Wyeth. Only one of the studies examined the effects of Losec 40mg and none looked at lansoprazole 60mg. All of the studies included omeprazole 20mg and lansoprazole 30mg. Three studies reported results favourable to lansoprazole 30mg compared to omeprazole 20mg (Dammann, Blum and Tollman) while three others reported that both doses were equivalent (Janczewska, Hedenström and Bruley Des Varannes). The Panel noted that the Seensalu data featured in the detail aid showed that in terms of acid suppression lansoprazole 30mg and omeprazole were comparable. The Panel considered that in terms of the other data the results from Seensalu were not unrepresentative and no breach of Clause 7.2 was ruled in that regard.

The Panel considered that it had not been made sufficiently clear that the data related to healthy volunteers. The Panel noted that it was an accepted principle under the Code that data which put claims into their correct clinical context must be prominently displayed if to do otherwise might give a misleading impression. A breach of Clause 7.2 of the Code was ruled.

## APPEAL BY ASTRA

Regarding the Panel's ruling that "The bar charts were misleading in breach of Clause 7.6 of the Code", Astra stated that this was made on the basis that inclusion of the additional lansoprazole data on acid suppression would have altered the perception created by the chart, as the study did not show significant differences between the doses Losec 40mg and lansoprazole 60mg, and the doses Losec 20mg and lansoprazole 15mg and lansoprazole 30mg. The omission of those data points was only misleading if they contradicted the balance of evidence.

In Astra's view the Panel appeared to rely on the principle that failure to demonstrate a statistically significant difference could be taken as conclusive evidence of equivalence between products and doses. Proof of equivalence was only possible if a study was designed specifically to demonstrate equivalence, ie either powered to detect a non clinically significant difference between groups or if the statistical analysis was performed to disprove the hypothesis that the studied groups were different (a reversal of the technique used in the Seensalu study). When small numbers of subjects were used, as in acid suppression studies, failure to demonstrate a statistically significant difference, while suggestive of equivalence, should not be regarded as proof of equivalence without either clinical corroboration (relevant in this context) or taking into account numerical trends in studies.

In the Seensalu study, the numerical trends when comparing Losec 20mg with lansoprazole 15mg and Losec 40mg with lansoprazole 60mg suggested a difference in favour of Losec over lansoprazole.

There were three other acid suppression studies which compared Losec 40mg daily and lansoprazole 60mg daily (Paoletti (1997), Timmer (1995) and Geus (1997)).

The numerical trends in favour of Losec 40mg vs lansoprazole 60mg in median 24 hr pH and % inhibition of 24 hr [$H^+$] AUC (bioavailability) in Seensalu were also reflected in the statistically significant differences (nocturnal median 24 hr pH, percentage of time in 24 hours pH>3, percentage of time at night pH>3, percentage of time in 24 hours pH>4 and percentage of night pH>4 in 24 hours) and numerical trends (all end points where statistically significant differences were not seen) in the Geus abstract 1997 and the full paper published in 1998.

The interpretation of the results from Paoletti was more problematic as the subjects involved were pre defined as having had a failure of Losec treatment. However to test relative efficacies of compounds in this group who had previously failed to respond to one of those compounds was reasonable. In this study numerical (time 24 hr pH>4, and time nighttime pH>4) and statistically significant differences (time 24 hr pH>3 and time nighttime pH>3) were seen in favour of lansoprazole 60mg.

Timmer (1995) compared Losec 20mg bd to lansoprazole 30mg bd in addition to comparisons with other lansoprazole doses. In this study lansoprazole 30mg bd was reported to be statistically significantly superior to Losec 20mg bd only in terms of time pH>3. Small non significant differences between Losec 20mg bd and lansoprazole 30mg bd were reported in terms of percentage time pH>5. The pharmacodynamic effects of Losec 20mg bd and lansoprazole 30mg bd were regarded as similar by the authors.

Losec 20mg had been compared to lansoprazole 15mg in acid suppression in one further study. Again, numerical differences in efficacy in favour of Losec 20mg over lansoprazole 15mg were seen (Meyer (1998)).

With reference to clinical corroboration: the presence of a clinically relevant difference in acid suppression between Losec 20mg and lansoprazole 15mg was supported by the only two clinical comparisons of these doses. In GORD healing (Castell (1996)) and maintenance (Baldi (1996)) Losec 20mg had been shown to be significantly more effective than lansoprazole 15mg.

Astra therefore believed that the data presented in the bar chart in the detail aid were not only in line with the referenced data but did not misrepresent the body of evidence. Astra therefore appealed against the Panel's ruling that the bar chart was in breach of Clause 7.6 of the Code.

Regarding the Panel's ruling that the heading "Losec can provide greater acid suppression than lansoprazole" was misleading and in breach of Clause 7.2, Astra said that this heading should be interpreted in the context of the data presented on the page. The doses were clearly identified in the graphical representation of the Seensalu study. In this representation acid suppression with Losec 40mg was seen to be significantly different from lansoprazole 30mg whereas there was no significant difference between Losec 20mg and lansoprazole 30mg. The purpose of the heading was to state that Losec could provide greater acid suppression than lansoprazole, ie not always and not across all doses of either Losec or lansoprazole. Astra therefore appealed the Panel's ruling that this heading was in breach of Clause 7.2.

Regarding the Panel's ruling of a breach of Clause 7.2 in that it had not been made sufficiently clear that the data related to healthy volunteers, Astra stated that the majority of acid suppression studies performed to date had been conducted in healthy volunteers rather than patients. While intragastric acidity in healthy volunteers might differ from that in ulcer patients, experience had shown that 24 hr pH recording in healthy volunteers was a suitable pharmacodynamic model to investigate the relative acid suppression potencies of differing regimes of proton pump inhibitors (Timmer (1995)). The fact that these comparisons in healthy volunteers were published in respected journals was supportive of their relevance in this area and to an audience of hospital specialists. It was Astra's belief that, in this context, the positioning of the study description, which specifically mentioned the nature of the subjects "16 healthy volunteers" was clear and did not mislead. Astra therefore appealed against the Panel's ruling of a breach of Clause 7.2.

## APPEAL BOARD RULING

The Appeal Board noted that the Seensalu study had examined the effect of three doses of lansoprazole, 15mg, 30mg and 60mg, but that only the results for the 30mg dose had been shown in the bar charts. Only two doses of Losec had been included in the study, 20mg and 40mg. The effect of 10mg had not been examined. The Appeal Board noted Astra's submission that the doses shown were clinically relevant for healing of acid related disorders and that Losec 10mg and lansoprazole 60mg were not licensed for healing. Zoton 60mg once daily was licensed for use in hypersecretory conditions. Zoton 30mg twice daily was licensed for *H.pylori* eradication therapy in combination with antibiotics.

The Appeal Board noted that the Seensalu data was from a study on 16 healthy volunteers. In terms of median 24 hour pH statistically significant differences had been shown between Losec 40mg and Losec 20mg and between Losec 40mg and lansoprazole 30mg and 15mg. Statistically significant differences between Losec 40mg and Losec 20mg and between Losec 40mg and lansoprazole 30mg had been shown for percentage inhibition of 24 hour intragastric activity. The Appeal Board did not accept Astra's submission that note should be taken of numerical differences. The Appeal Board considered that in the circumstances the use of selected doses was unacceptable. If all the results had been shown readers would have seen that there was no statistical difference between Losec 40mg and lansoprazole 60mg nor between Losec 20mg and lansoprazole 15mg or 30mg. The Appeal Board considered that the bar charts based on such data were misleading and upheld the Panel's ruling of a breach of Clause 7.6 of the Code.

The appeal on this point failed.

With regard to the page heading "Losec can provide greater acid suppression than lansoprazole" the Appeal Board considered that most readers would interpret it to mean that Losec always provided greater acid suppression. The Appeal Board did not consider that the use of the word "can" was enough to qualify the claim and upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal on this point failed.

The Appeal Board considered that it had not been made sufficiently clear that the acid suppression data had been taken from healthy volunteers and was, therefore, physiological as opposed to clinical, data. The Appeal Board noted the supplementary information to Clause 7.2 which stated that care must be taken so as not to mislead as to the significance of data taken from volunteer studies. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 in this regard.

The appeal on this point failed.

### 3 Heading "Losec 40mg daily can provide greater acid suppression than lansoprazole 60mg daily"

This page featured three bar charts depicting various parameters relating to gastric acidity as measured in a study by Geus *et al* (1997).

#### COMPLAINT

Wyeth alleged that this page was in breach of Clause 7.2. The implication was that Losec 40mg was more potent than lansoprazole 60mg. As previously stated in point 2, the evidence available did not support this. This statement was therefore misleading so breaching Clause 7.2.

The statement: "At high daily doses licensed for *H.pylori* eradication" and the subsequent graphical presentations of the referenced data (Geus *et al* (1997)) suggested that for *H.pylori* eradication Losec 40mg was a better choice than lansoprazole 60mg. The data portrayed on this page was misleading and failed to take into consideration all the available data. Wyeth provided a copy of a paper by Timmer *et al* (1995) which had originally appeared as an abstract by Ripke *et al* (1995).

Successful *H.pylori* eradication required a pH greater than 5. Unfortunately the referenced data reported only on pH levels greater than 3 and 4 and was therefore irrelevant and misleading in the context of *H.pylori* eradication. Selective use of data was again evident, the study by Timmer *et al* comparing the same doses of drug, and evaluating the length of time spent above pH 5, was not mentioned. A breach of Clause 7.2 was alleged.

Wyeth had the same comments with regard to the positioning of the statement on "healthy volunteers" as in point 2.

#### RESPONSE

Astra said that the data represented from the Geus study showed that Losec could provide greater acid suppression than lansoprazole ie not always and not across all doses. The claim was, therefore, qualified and Astra rejected any breach of Clause 7.2 as there was no intention to mislead with this statement.

Regarding the contention that Losec 40mg was more potent than lansoprazole 60mg, the data supplied were representative of all the study data; at the doses relevant to *H.pylori* eradication, the numerical trends were always in favour of Losec 20mg bd vs lansoprazole 30mg bd.

Regarding the statement by Wyeth that successful *H.pylori* eradication required a pH greater than 5, the Ripke abstract, designed to investigate acid suppression in *H.pylori*, made no mention of this fact, indeed the result for percentage of time intragastric pH was greater than 3 was emphasised. Successful *H.pylori* eradication required the combination of effective acid suppression and appropriate antibiotic therapy; in this context it was relevant to present data which reflected the wider picture of acid suppression rather than concentrating on one specific endpoint. Data on pH levels greater than 3 and 4 were therefore indeed relevant and not misleading.

The Ripke study found no significant differences at pH greater than 5 across all lansoprazole doses (ranging from 30mg od to 60mg bd) and omeprazole 20mg bd; it also reported lansoprazole 30mg bd to be significantly superior to omeprazole 20mg bd regarding the percentage of time in 24 hours greater than pH 3. However, the confounding variable of *H.pylori* status was not considered which was a critical factor in evaluating outcome. This potentially invalidated the Ripke findings as *H.pylori* positive or negative status was known to affect gastric acid secretion. In contrast, in the Geus study, the volunteers were clearly stated as *H.pylori* negative. The Geus data had therefore been justifiably chosen for illustration.

Regarding the comments on positioning and use of "healthy volunteers" Astra referred to its previous comments made in point 2.

Astra rejected that a breach of Clause 7.2 had occurred.

#### PANEL RULING

The Panel noted that the heading referred to the fact that Losec 40mg "can provide greater acid suppression". The Panel did not accept Astra's submission that the claim was qualified by the use of the word can. In the Panel's view readers would interpret the claim as meaning that the greater acid suppression would happen always. The only data presented (Geus *et al* (1997)) demonstrated a difference between Losec and lansoprazole, in favour of Losec, which reinforced the impression that there would always be a difference and this was not so. The Panel ruled a breach of Clause 7.2 of the Code.

The Panel noted that one of the bar charts illustrating the Geus data showed the percentage of time that intragastric acidity was greater than pH 3. The chart showed a statistically significant result in favour of omeprazole 20mg bd compared with lansoprazole 30mg bd. These results were contrary to the earlier results of Timmer *et al* (1995). The Panel noted that the Geus paper stated that the healthy subjects who had taken part in the study were all *H.pylori* negative. This fact was given in small print in the description of the study which followed the reference. The *H.pylori* status of the healthy volunteers in the Timmer study was unknown. The Panel noted that Timmer *et al* had commented that their results in healthy volunteers had to be confirmed in *H.pylori* positive patients in appropriate clinical trials. The Panel considered that the presentation of the Geus study which had been carried out on *H.pylori* negative controls under the statement "At high daily doses licensed for *H.pylori* eradication" was confusing given Astra's submission that *H.pylori* status was known to affect gastric acid supression. Overall the Panel considered that the data presented did not represent the balance of the evidence and ruled a breach of Clause 7.2.

The Panel noted that on the bar chart showing the percentage of time that intragastric pH was greater than 3 over a 24 hour period the p value was given as less than 0.05 whereas the original abstract had stated the p value was equal to 0.05. The Panel requested that this error was drawn to Astra's attention.

The Panel considered its ruling of a breach of Clause 7.2 in point 2 regarding the healthy volunteer data also applied here.

### APPEAL BY ASTRA

Regarding the Panel's ruling that the heading "Losec 40mg daily can provide greater acid suppression than lansoprazole 60mg" was in breach of Clause 7.2, Astra referred to its previous comments regarding the interpretation of data from small sample sizes which might not be statistically significant. In addition it had the following comments.

The data represented from the Geus study showed that Losec could provide greater acid suppression than lansoprazole, ie not always and not across all doses. The heading was specifically qualified by the inclusion of the Losec 40mg and lansoprazole 60mg doses. Only these doses were used in the text below, highlighting where this difference could be seen.

Regarding the contention that Losec 40mg was more potent than lansoprazole 60mg, the Geus data depicted were representative of all the study data; at the doses relevant to *H.pylori* eradication, the numerical trends were always in favour of Losec 20mg bd vs lansoprazole 30mg bd.

With regard to the body of evidence for the comparison of lansoprazole 30mg bd and Losec 20mg bd, Astra referred to its previous comments on the studies by Seensalu, Timmer and Paoletti. It believed that, while the number of studies was not large, the data presented in the bar chart in the detail aid did not misrepresent the body of evidence.

Astra therefore appealed against the Panel's ruling that the headline was in breach of Clause 7.2.

Regarding the Panel's ruling of a breach of Clause 7.2 in that it had not been made sufficiently clear that the data referred to healthy volunteers, Astra referred to its previous comments. It also commented that this data had subsequently been published in Alimentary Pharmacology & Therapeutics, a well respected specialist journal. It was Astra's belief that the intended audience was used to the interpretation of healthy volunteer data in this context.

Astra therefore appealed against the Panel's ruling of a breach of Clause 7.2.

### APPEAL BOARD RULING

The Appeal Board noted that the heading stated that "Losec 40mg daily can provide greater acid suppression than lansoprazole 60mg daily". The Appeal Board did not consider that the word "can" was enough to qualify the heading and considered that most readers would interpret it to mean "Losec 40mg daily provides greater acid suppression than lansoprazole 60mg daily". The Appeal Board considered that the heading was misleading and upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal on this point failed.

The Appeal Board noted that the Geus data had been taken from healthy volunteers. The Appeal Board noted that running through the detail aid, at the bottom of every right hand page and at the bottom of the page in question, was the strapline "Powerful acid suppression. Powerful clinical response". The Appeal Board considered that it had not been made sufficiently clear that the acid suppression data was from a physiological as opposed to a clinical study. Its ruling in point 2 regarding healthy volunteer data also applied here. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal on this point failed.

## 4 Heading "Increasing acid suppression increases clinical response"

### COMPLAINT

Wyeth alleged that this page was in breach of Clause 7.2. The data presented focused on the healing of duodenal ulcers. The recognised cornerstone of successful duodenal ulcer treatment was the eradication of *H.pylori* – not the use of 4 weeks' acid suppression. To suggest otherwise was both inaccurate and misleading.

### RESPONSE

Astra said that the data presented supported greater acid suppression with Losec 40mg than Losec 20mg and a higher percentage of patients healed of their duodenal ulcer with Losec 40mg compared directly with Losec 20mg. The text in no way diminished the relevance of *H.pylori* eradication which was clearly highlighted in the detail aid. Astra also pointed out that this detail aid was for use with an expert audience who would be well aware of the current management of this condition. To not include the important aspect of treatment of duodenal ulcer in a discussion of the use of Losec in acid related disorders would be inappropriate. As mentioned earlier, the Losec detail aid was tested with hospital physicians to ensure that the layout was clearly understood.

In this context, Astra did not believe the data presented misled (by suggesting 4 weeks' acid suppression to be more relevant than *H.pylori* eradication) and therefore rejected any breach of Clause 7.2.

### PANEL RULING

The Panel noted that the preceding pages of the detail aid had concentrated on the acid suppression achieved with Losec 40mg. The page in question presented the clinical response that might be achieved with Losec 40mg, ie the healing of duodenal ulcers. In the Panel's view it was acceptable to present such data. The Panel noted that the usual dose for the healing of duodenal ulcers was 20mg Losec daily with the majority of patients being healed after 4 weeks. In severe or recurrent cases the dose could be increased to 40mg Losec daily. Although the importance of *H.pylori* eradication was not mentioned on the page in question the intended audience would be aware of it. The healing of duodenal ulcers was nevertheless one important aspect. The Panel did not accept the allegation and no breach of the Code was ruled.

The Panel noted that the data presented had been taken from Lauritsen *et al* (1992) and a bar chart showed that the percentage of duodenal ulcer patients healed at two weeks was comparable for both Losec 20mg and Losec

40mg (63.9% vs 69.9%). At four weeks there was a statistically significant difference in favour of Losec 40mg (93.9% vs 88.6%). A claim above the bar chart stated that "A greater number of duodenal ulcer patients were healed at 4 weeks with Losec 40mg od than with Losec 20mg od". The Panel noted that the authors of the study indicated that this difference might be of minor clinical importance. The conclusion of the study stated that "... 20mg of omeprazole is an appropriate dosage for most patients with duodenal ulcer. In the few patients with an unhealed ulcer after 8 weeks of treatment, a dose of 40mg omeprazole may be considered". The Panel considered that the way in which the Lauritsen data had been presented, ie to support the use of Losec 40mg at the outset of treatment, did not accurately reflect the opinions of the authors. The Panel noted that 40mg was the daily dose of Losec in *H.pylori* eradication in duodenal ulcer or gastric ulcer disease with antibiotics as either dual or triple therapy. It would have been helpful if this had been made clear on the page in question. In addition the Panel considered that the page did not accurately reflect the SPC for Losec and requested that Astra be advised of its views.

## 5 Heading "Lansoprazole does not offer dose dependent healing"

### COMPLAINT

Wyeth alleged that this page was in breach of Clauses 7.2 and 8.2. Lansoprazole 30mg dose was the optimum dose for healing; to suggest that this was an issue was both misleading and disparaging. The data also focused on duodenal ulcer healing; as stated previously in point 4 the cornerstone of successful duodenal ulcer treatment being eradication therapy rather than acid suppression alone.

The trial referenced (Avner *et al* (1995) had also been carefully selected to give the lowest 2 and 4 week healing rates seen in any lansoprazole study [Bardhan *et al* (1995) was also cited]. No mention was made of the studies which did show dose dependent healing, these covered a dose range of 7.5 - 60mg and clearly showed that dose dependent healing did occur up to a maximum dose of 30mg (Hawkey *et al* (1993); Aaronson *et al* (1991); Londong *et al* (1991) and Licht and Lemaire (1990)).

This was yet another selective use of all the available data.

It seemed (as pages 4 and 5 formed a double page spread) that the intention was to invite comparison between the lansoprazole and omeprazole data. The studies were picked to make the most dramatic comparison between the two in favour of omeprazole.

The selective use of these data was misleading and disparaging in suggesting that lansoprazole was inferior to omeprazole in terms of healing rates in breach of Clauses 7.2 and 8.2.

### RESPONSE

Astra said that the detail aid did not suggest that the lansoprazole 30mg dose was not the optimum lansoprazole dose for healing. It pointed out that it was the only licensed dose for healing. The "issue" highlighted was the lack of dose-dependent healing seen with lansoprazole and this was actually supported by the references as quoted by Wyeth. Indeed, Wyeth itself stated that its quoted study references only showed dose-dependent healing up to a maximum of 30mg not 60mg, at lower doses lansoprazole was either equal to, or less efficacious than, the only licensed healing dose of lansoprazole, 30mg.

The relevant data were summarised as follows:

Hawkey *et al* compared duodenal ulcer healing rates for lansoprazole 30mg, lansoprazole 60mg and ranitidine 300mg. Whilst both lansoprazole 30mg and 60mg were associated with faster ulcer healing and better symptom relief than ranitidine 300mg, there were no significant differences between lansoprazole 30mg and 60mg.

Aaronson *et al* reported similar duodenal ulcer healing rates for lansoprazole 15mg, 30mg and 60mg. At week 2, rates were 42.4%, 35.6% and 39.1% respectively (highest at 15mg); at week 4, rates were 89.4%, 91.7% and 89.9% respectively (highest at 30mg). Dose-dependent healing was not therefore demonstrated.

Both Londong *et al* and Licht and Lemaire only studied doses of lansoprazole up to 30mg; no data on lansoprazole 60mg were generated for comparison. The Londong trial only found significant differences between the healing rates reported with lansoprazole 7.5mg and 30mg and notably not between 15mg and 30mg. This was not clinically relevant as neither 7.5mg or 15mg were licensed healing doses of lansoprazole. Londong also reported no significant differences in relapse rates after lansoprazole 7.5mg, 15mg and 30mg (21%, 29% and 22% respectively) further supporting a lack of dose-response with lansoprazole.

The Licht and Lemaire study reported a more rapid response with lansoprazole 30mg than 15mg or 7.5mg and higher duodenal ulcer healing rates but again a 60mg dose of lansoprazole was not studied and therefore no comparisons with the 60mg dosage might be made.

Returning to the detail aid, the statement that the healing rates for both duodenal ulcer and reflux oesophagitis did not differ significantly for the 30mg and 60mg doses of lansoprazole also reflected accurately the conclusions reached in the studies performed by Avner *et al* and Bardhan *et al* respectively. Avner *et al* stated that the dose-dependent action of lansoprazole was not reflected in the duodenal ulcer healing rates found in their study; no statistically significant differences were found in the healing rates at 2 or 4 weeks with lansoprazole 15, 30 or 60mg daily. Indeed, 15mg lansoprazole was shown to be as effective as the higher doses at both 2 and 4 weeks of treatment. Turning to reflux oesophagitis both mild and severe, Bardhan *et al*, in a review of the available data, reported no significant differences in the healing rates achieved with 30mg and 60mg doses of lansoprazole.

The lack of any clinically significant dose-response with lansoprazole in both duodenal ulcer and reflux oesophagitis was therefore supported by the findings from the quoted studies in the detail aid and was a valid conclusion from the data. It therefore could not be construed as a covert attempt to suggest any lack of efficacy *per se* for lansoprazole at its licensed dosage, but

implied no differences in healing rates for the 30mg and 60mg doses of lansoprazole. This was a statement of fact and was not disparaging.

In summary, the data quoted were neither selective nor disparaging . They were consistent with the findings from the Wyeth-quoted studies and showed a lack of dose-dependent healing between lansoprazole 30mg and 60mg, as claimed in the detail aid. These data did not suggest that lansoprazole was inferior to omeprazole in terms of healing rates and a breach of Clauses 7.2 and 8.1 (implied) was rejected. Wyeth also alleged that the piece breached Clause 8.2 of the Code. The reasons for this allegation were unclear as there was no reference to the health professions or their clinical and scientific opinions within the piece. A breach of Clause 8.2 was, therefore, also rejected.

## PANEL RULING

The Panel noted that the page in question, headed "Lansoprazole does not offer dose-dependent healing" featured a bar chart comparing the percentage of patients with a healed duodenal ulcer after 2 and 4 weeks' treatment with lansoprazole 30mg or 60mg. After 4 weeks' treatment the percentage of patients healed on 30mg was 89.3% and that on 60mg was 87.7%. There was no statistically significant difference between the two. The Panel noted that above the bar chart was the statement that "Lansoprazole 30mg is the only licensed dose for healing" which was in accordance with the product data sheet. The Panel questioned the clinical relevance, therefore, of including data on the 60mg dose.

The Panel noted that the healing rate given for lansoprazole 30mg in the detail aid was 89.3% after 4 weeks. The four papers cited by Wyeth (Hawkey *et al*; Aaronson *et al*; Londong *et al* and Licht and Lemaire), however, reported healing rates of between 91% and 95% after 4 weeks' treatment with lansoprazole 30mg. The two papers cited in the detail aid, however, reported healing rates of less than 90%.

The Panel noted that the bar chart for lansoprazole appeared on the page opposite a similar chart for Losec. The Panel considered that such a layout would invite direct comparison of the two products in favour of Losec. The Panel noted that the healing rate for Losec 40mg was 93.9% after 4 weeks whereas that shown for lansoprazole 30mg was 89.3%. There was data, however, to show comparable healing rates between the two.

The Panel considered that the page in question was misleading as a 60mg dose was not relevant to the licensed indication and the bar chart depicted one of the lowest 4 week healing rates reported with lansoprazole 30mg. The layout of the page invited a direct but unfair comparison with Losec. A breach of Clause 7.2 was ruled.

In the Panel's view the heading "Lansoprazole does not offer dose dependent healing" implied that this was a disadvantage. The Panel noted that 30mg lansoprazole, the dose licensed for the healing of duodenal ulcers, achieved healing rates comparable to that of Losec. The question of dose dependent healing appeared irrelevant. The page in question was opposite the page for Losec which did show dose dependent healing and in the Panel's view the layout implied that lansoprazole was not as effective as Losec. The Panel considered that the page disparaged lansoprazole and ruled a breach of Clause 8.1 of the Code. (In the Panel's view Wyeth had alleged a breach of Clause 8.2 when it had meant to cite Clause 8.1. No ruling regarding Clause 8.2 was made.)

## APPEAL BY ASTRA

With regard to the Panel's ruling that the page headed "Lansoprazole does not offer dose-dependent healing" was in breach of Clause 7.2 on the basis that lansoprazole 60mg was not licensed in any peptic ulcer healing indication, that the bar chart depicted one of the lowest 4 week healing rates for lansoprazole at 89.3% and that the layout of the page invited a direct but unfair comparison between the two drugs, Astra said that Losec was licensed for healing of duodenal and gastric ulcers at 20mg and the Losec SPC stated that in severe or recurrent cases of benign peptic ulcer the dose of Losec might be increased to 40mg.

Lansoprazole was licensed for healing in the same indications at 30mg but not 60mg. The lack of a licence for healing at the 60mg dose was a clinically valid differentiation point between the two medicines. Losec 20mg had been shown to be not significantly different to lansoprazole 30mg in the healing of duodenal ulcer at 4 weeks (Ekström (1992), Capurso (1995), Chang (1995)). For further healing, the clinician had the option to increase the dose of Losec to 40mg whereas upward dose titration with lansoprazole did not have any additional effect and was not licensed. Increased healing above Losec 20mg was thus relevant to the licence and in context.

The bar chart depicted a healing rate for lansoprazole 30mg of 89.3% at 4 weeks. Healing rates at 4 weeks with lansoprazole 30mg in duodenal ulcer studies ranged from 76.2% (Lanza (1994)) to 97.1% (Ekström (1995)).

Only two published studies examined lansoprazole 30mg and 60mg together (Avner (1995) and Hawkey (1993)) and they failed to show a dose response. Comparison of healing rates from different patient groups in different populations, studied at different times, by different investigators, was difficult due to the possibilities of bias arising. Of the studies performed the lowest healing rate at 4 weeks in percentage terms was 76.2% (Lanza (1994)). The highest (Ekström (1992)) was 97.1% patients healed. The differences in healing rates were indicative of the high intra-study variability that occurred when comparing end points. The Avner study, with a healing rate of 89.3% after 4 weeks, was not unrepresentative in this regard.

The Lauritsen and Avner studies were clearly presented on separate pages of the detail aid, under different headings with separate references. A comparison of the two studies might be made in the knowledge that there were two separate studies: this was not unfair given the lack of any single study which compared Losec 20mg and 40mg with lansoprazole 30mg and 60mg in this indication. Astra therefore appealed against the Panel's ruling of a breach of Clause 7.2.

Regarding the Panel's ruling of a breach of Clause 8.1 in that the page disparaged lansoprazole, Astra referred to

its previous comments above on this matter and appealed against the Panel's ruling of a breach of Clause 8.1.

### APPEAL BOARD RULING

The Appeal Board noted that that first statement on the page was "Lansoprazole 30mg is the only licensed dose for healing". Data was then presented regarding the healing rate observed using a lansoprazole dose of 60mg. The Appeal Board noted that Losec 20mg was the licensed dose in healing. The dose of Losec 40mg was to be used in gastro-oesophageal reflux disease refractory to other therapy or in severe or recurrent gastric ulcer or duodenal ulcer. The Appeal Board noted that page four of the detail aid stated that the four week healing rates for Losec 20mg and 40mg were 88.6% and 93.9% respectively. The four week healing rate for lansoprazole 30mg, on page five of the detail aid, was 89.3%. The Appeal Board noted that the four week healing rate for lanzoprazole had been reported to be as much as 97.1% in some patient groups. In the Appeal Board's view the four week healing rates for Losec 20mg and 40mg and lansoprazole 30mg were comparable. That there was no greater healing rate achieved using an unlicensed dose of lansoprazole was irrelevant. The page was misleading and the Appeal Board therefore upheld the Panel's ruling of a breach of Clause 7.2.

The appeal on this point failed.

The Appeal Board considered that the heading "Lansoprazole does not offer dose-dependent healing" implied that this was a disadvantage and disparaged Zoton. The Appeal Board upheld the Panel's ruling of a breach of Clause 8.1.

The appeal on this point failed.

## 6 Heading "High acid suppression for high healing rates in duodenal ulcer"

### COMPLAINT

Wyeth alleged that this page was in breach of Clause 7.2. As stated previously in point 4, the cornerstone of successful duodenal ulcer treatment was eradication therapy rather than acid suppression alone.

### RESPONSE

This was a reiteration of point 4 to which Astra had already responded. It was clinically relevant to present the relationship between acid suppression and duodenal ulcer healing rate. The allegation that this page was in breach of Clause 7.2 was denied.

### PANEL RULING

The Panel noted that the page in question examined the relationship between acid suppression and rates of duodenal ulcer healing with Losec, ranitidine and cimetidine. In the Panel's view it was acceptable to present such data. Although the importance of *H.pylori* eradication was not mentioned the intended audience would be aware of it. No breach of the Code was ruled.

## 7 Heading *"Helicobacter pylori* eradication in 7 days"

This page presented data on the rates of eradication of *H.pylori* seen with Losec (omeprazole) in combination with various antibiotics. Data on three triple therapies was presented: Losec/ amoxycillin/metronidazole (OAM) from Bell *et al* (1995); Losec/clarithromycin/ metronidazole (OCM) and Losec/amoxycillin/ clarithromycin (OAC) from Lind *et al* (1996).

### COMPLAINT

Wyeth alleged that this page was in breach of Clauses 7.2, 7.8 and 8.2. The headline *"Helicobacter pylori* eradication in 7 days" was an all embracing claim and breached Clause 7.8. It implied that at the end of a 7 day period *H.pylori* would have been eradicated in all patients which was not the case.

The initial statement regarding Losec was "... high acid suppression for healing duodenal ulcer ...".

The overall implication from this statement (when combined with the page headline) seemed to be that the duodenal ulcer would have been healed at the end of the 7 day treatment course. There were several points which Wyeth considered needed to be addressed:

a) Wyeth did not believe that Astra had a licence for duodenal ulcer healing following 7 days' eradication therapy.

b) The paper to which the above statement on healing was referenced, Jones *et al* (1987), related to a 4 week healing study with acid suppression, and not an eradication study.

Wyeth believed the data portrayed on this page in relation to successful *H.pylori* eradication rates was also misleading:

a) The eradication rates given did not appear to be representative of all the data available. Additional work on the OCM and OAC regimens was not presented here (Lind *et al* (1997)).

b) The Losec dose used in the study referenced, Lind *et al* (1996), was 20mg bd. Listing this as 40mg/day was misleading.

c) The patient population studied by Bell et al (1995) had endoscopically confirmed duodenal ulcer, gastric ulcer or non-ulcer dyspepsia. However the triple therapy regimen referred to (OAM) was licensed for eradication in duodenal ulcer only, to report on patients with other *H.pylori* positive conditions was outside of the licence terms.

d) The Bell study was also single centre open. Given the recent focus on the credibility of *H.pylori* eradication studies and the requirement for them to be multi-centre, double-blind etc, the use of this particular study seemed inappropriate.

e) No mention was made of which statistical analysis was presented. Lind gave three alternative statistical analyses.

### RESPONSE

Astra said that as described by Wyeth, this was a headline

not an all-embracing or superlative claim. It did not imply eradication in all patients at the end of 7 days. On the contrary, the detail aid clearly and prominently quoted eradication rates of 91.1%, 95% and 96% respectively from 3 separate studies using Losec 40mg in combination with different antibiotic regimes, as highlighted in the detail aid (Bell *et al*, Lind *et al*, Jones *et al*).

The statement regarding "High acid suppression for healing duodenal ulcer ...." and the title "*Helicobacter pylori* eradication in 7 days" were not, a priori, linked together. It was only by taking this part of the full sentence out of its correct context that this impression could be gained. The full sentence was as follows:

"Losec 40mg offers the combination of:

- high acid suppression for healing duodenal ulcer with a range of antibiotics to effectively eradicate *Helicobacter pylori*".

The clear statement was that Losec 40mg brought together two important facets of the treatment of duodenal ulcer disease, high acid suppression and combination therapy. No claim was made for duodenal ulcer healing after only 7 days *H.pylori* eradication therapy, nor was this implied. No medicinal product was specifically licensed for duodenal ulcer healing following only 7 days' eradication therapy.

Regarding the use of the Jones reference, this was a meta analysis of healing rates to examine the optimal dosing of anti-secretory drugs and its relation to acid suppression, the reference supported the statement "High acid suppression for healing duodenal ulcer" which was a statement of fact. The statement "a range of antibiotics to effectively eradicate *Helicobacter pylori*" was separately and clearly referenced, this was again a statement of fact. As previously stated, the full body of the copy, in bringing together these important aspects of therapy of duodenal ulcer disease, was not misleading and inappropriate; this was supported by Astra's market research with hospital physicians.

The statement of high acid suppression clearly related to duodenal ulcer healing and was therefore no more than a statement of fact. In view of the facts that duodenal ulcer was a condition commonly associated with *H.pylori*, and that acid suppression was a key part of successful treatment, it was relevant to mention it here.

It was only by taking this information out of context that the data presented could be misconstrued as promoting the product for duodenal ulcer healing following eradication or that the referencing could be deemed inappropriate. The allegations were, therefore, rejected.

Regarding the data relating to *H.pylori* eradication rates and the five points (a-e) raised by Wyeth:

a) The detail aid represented accurately the Lind (1996) data (MACH 1 study). The "all patients treated" (APT) analysis presented in the detail aid was not represented in the abstract of the MACH 2 [Lind (1997)] study mentioned by Wyeth and was, therefore, representative of the body of evidence.

The eradication rates for the studies in respect of both the "intention to treat", "per protocol" and APT (where included) analyses were similar and the additional work on the OCM and OAC regimens was comparable.

The data presented in the detail aid encompassed the licensed regimens for *H.pylori* eradication therapy and had been presented for this reason. The data from the MACH 1 study was comparable to the data from the MACH 2 study referred to by the complainant.

Astra, therefore, rejected any allegation that the data included was misleading.

b) Listing the dose as 40mg/day was not intended to mislead. The Losec dose was 20mg bd ie a daily dose of 40mg. Both 40mg od and 20mg bd were licensed regimens for Losec in *H.pylori* eradication.

c) The Bell data was used as an illustration of the *H.pylori* eradication rates that could be achieved using Losec in combination with antibiotics, as was the other data on this page. The clear intention was to give examples of eradication rates, not to promote outside the licence.

d) Not only was the study author well respected in the field of *H.pylori* eradication, but the study was peer reviewed and published in a respected journal. The quotation of the data generated was highly appropriate as part of the body of world literature on the subject.

e) The findings were comparable using either an "intention to treat" or "per protocol" analysis. There were no major differences in eradication rates using different statistical analyses.

The allegations of breaches of Clause 7.2, 7.8 and 8.2 were rejected. Any breach of Clause 8.1 was also denied.

## PANEL RULING

The Panel did not consider that the headline "*Helicobacter pylori* eradication in 7 days" implied that at the end of 7 days *H.pylori* would have been eradicated in all patients. The Panel noted that the data sheet for Losec stated that the product was indicated for *H.pylori* eradication, in combination with antibiotics, and gave details of seven day regimens. It was, therefore, reasonable to refer to *H.pylori* eradication in seven days but the Panel did not consider that given the therapy area and the intended audience the headline would be read to mean that Losec had a 100% success rate in seven days. The graphs featured on the page below quite clearly depicted seven day eradication rates of less than 100%. No breach of Clause 7.8 was ruled.

Directly below the headline was the claim that Losec offered the combination of high acid suppression for healing duodenal ulcer with a range of antibiotics to effectively eradicate *H.pylori*. The Panel noted that the headline referred to *H.pylori* eradication in 7 days but the claim made no mention as to the rate of either duodenal ulcer healing or *H.pylori* eradication. The Panel did not consider that the claim regarding duodenal ulcers implied a healing rate of seven days. The seven day period was clearly linked only to *H.pylori* eradication. In addition the Panel noted that the three preceding pages had referred to duodenal ulcer healing after 4 weeks' therapy. In the Panel's view readers would not now assume that duodenal ulcers would be healed in 7 days. No breach of Clause 7.2 was ruled.

The Panel noted that the detail aid featured *H.pylori* eradication rates of 95% for OCM therapy and 96% for OAC therapy. These results were the eradication rates for the all-patient analysis reported by Lind et al (1996). Two other statistical analyses had been included in the paper: a per protocol analysis gave eradication rates of 94% and 98% for OCM and OAC therapy respectively while an intention to treat analysis gave rates of 90% and 91% respectively. The Panel noted that an abstract reporting further work on the OCM and OAC regimens, Lind *et al* (1997), included a per protocol analysis and an intention to treat analysis and while figures for the two regimens differed slightly from those published in 1996 they were broadly similar. The Panel noted that the abstract contained the statement that its results confirmed those of the earlier paper. The Panel considered that the data shown in the detail aid was balanced and no breach of Clause 7.2 was ruled.

The Panel noted that the Losec dose used in the study by Lind *et al* (1996) had been 20mg bd. In the detail aid the dose was given as 40mg/day. While the Panel considered that it might have been helpful to give the specific dosage it noted that 40mg/day was not incorrect. No breach of Clause 7.2 was ruled.

The Panel noted that the data sheet for Losec stated that OAM therapy was indicated as *H.pylori* eradication therapy only for patients with duodenal ulcers. The OAM data reported in the detail aid had included patients with duodenal ulcers, gastric ulcers and non-ulcer dyspepsia (Bell *et al* (1995)). The Panel noted that for this group of patients the *H.pylori* eradication rate for OAM therapy was 91.1%. Figures for the eradication rate only in patients with duodenal ulcers was not available. The Panel considered that to quote a specific eradication rate that included patients other than those for which OAM therapy was indicated was misleading and in breach of Clause 7.2 of the Code.

The Panel noted that the description of the work by Bell *et al* lacked any details regarding the design of the study. It was a single centre open study. The Panel considered that it would have been helpful to include such details but their omission did not mislead. No breach of Clause 7.2 was ruled.

The Panel noted that no details were given regarding the statistical analyses presented. Lind *et al* (1996) had used three types of statistical analysis: all-patient; intention to treat and per protocol. The Panel noted that the results were similar whichever statistical analysis had been used. The Panel did not consider that the failure to specify which analysis had been used misled. No breach of Clause 7.2 was ruled.

### APPEAL BY ASTRA

Regarding the Panel's ruling that to quote a specific eradication rate that included patients other than those for which OAM therapy was indicated was misleading and in breach of Clause 7.2, Astra stated that it believed that the Panel had made an error in the statement that the data sheet for Losec stated that OAM therapy was indicated as *H.pylori* eradication therapy only for patients with duodenal ulcers. Losec was indicated as follows in *H.pylori* eradication: "Omeprazole should be used in combination with antibiotics for eradication of *Helicobacter pylori* (Hp) in peptic ulcer disease. Relief of associated symptoms", ie Losec was licensed in this indication for gastric and duodenal ulcers. Furthermore, the Bell *et al* data were used specifically to support the OAM regime in the clinical expert report for the Losec licence application for this indication. This product licence application was reviewed by the CSM and led directly to the granting of a licence for the Losec/OAM regime in peptic ulcer. The study was large, used the appropriate regime and was conducted in a UK population. The data was, therefore, relevant in this discussion.

Astra therefore appealed against the Panel's ruling of a breach of Clause 7.2.

### APPEAL BOARD RULING

The Appeal Board examined the Losec 40mg SPC. The indications referred to the use of omeprazole in combination with antibiotics for eradication of *H.pylori* in peptic ulcer disease. Section 4.2 of the SPC gave dosage particulars for dual therapy in duodenal ulcer disease and gastric ulcer disease. Triple therapy regimens were only for duodenal ulcer disease. No mention was made of the use of triple therapy in gastric ulcer disease.

The Appeal Board noted that the Bell study had included patients with duodenal ulcers, gastric ulcers and non-ulcer dyspepsia. According to Astra the patients were evenly distributed across the three conditions. Patients had received triple therapy with omeprazole, amoxycillin and metronidazole. The Appeal Board noted that triple therapy was not a licensed regimen for patients with gastric ulcers. The Bell data had thus included patients for whom the regimen used was unlicensed. In the Appeal Board's view it was misleading to quote a specific eradication rate that included patients other than those for which OAM was indicated. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2.

The appeal on this point failed.

## 8 Heading "In a highly acid sensitive condition: erosive reflux oesophagitis"

### COMPLAINT

Wyeth alleged that this page was in breach of Clauses 7.2 and 7.5. The headline clearly indicated that this page dealt with erosive reflux oesophagitis, as did the sub-heading and the graphical representation of data from Jaspersen *et al* (1997). It was only when reading the "title" of the reference at the bottom of the page that it became apparent that the study dealt with the much rarer condition of reflux complicated by strictures. By implication any results would be potentially misleading, so breaching Clause 7.2.

The graph showed the "Percentage of oesophagitis patients healed at 12 weeks" following randomization to Losec, lansoprazole and pantoprazole after an initial 6-8 weeks' treatment with Losec (not mentioned in graph). The implication was that only 20% lansoprazole patients were likely to remain in remission, compared to 90% of Losec patients. This was in contrast to a study by Swarbrick *et al* (1996), in which a similar population of

patients with reflux oesophagitis, complicated by a stricture, received treatment with lansoprazole 30mg. Results showed that 77% patients had no dysphagia at 6 months.

Astra was again showing selective use of data, and made no mention of an alternative study which gave contradictory results, so breaching Clause 7.2.

Patients were all initially treated with Losec in a healing phase before they entered the maintenance phase. Whilst Wyeth accepted that this was normal practice, it would naturally lead to a bias towards the Losec population who were maintained on the same medication and this should have been mentioned in the graph. It could also go some way to explaining the results which were in contrast to the Swarbrick study. Wyeth believed that the randomisation was open, so introducing obvious bias.

Wyeth felt that these facts alone ensured that this page did not represent a balanced view, and was also misleading so breaching Clause 7.2.

To suggest that the data in the study referenced to Jaspersen was representative of current medical practice was both misleading and insulting to the medical profession, and so breached Clauses 7.2 and 8.2. Reflux oesophagitis was known to be a chronic relapsing condition, some 80% of patients would relapse within 6 months if not given some form of maintenance treatment. This became even more important when complicated by strictures if regular re-dilation was to be avoided.

## RESPONSE

Astra said that the headline (erosive reflux oesophagitis), the claim (complicated reflux oesophagitis) and the reference (complicated reflux oesophagitis with stricture) were consistent in their referral to the severity of the reflux and the fact that the oesophagitis was complicated. A breach of Clause 7.2 under the broad statement "by implication any results would be potentially misleading" was therefore, rejected.

The graphically depicted findings were a true representation of the Jaspersen data.

Comparison with the findings of Swarbrick *et al* was not appropriate as the end points assessed were quite different: Jaspersen assessed the percentage of oesophagitis patients healed at 12 weeks, this end point based on the number of patients without oesophagitis, stricture or symptoms; Swarbrick *et al* conducted a 12 month trial in oesphagitis patients with stricture and assessed time to recurrence based on the requirement of at least one dilation during the 12 month period - a completely different end point. The reports from Swarbrick *et al* of lower dysphagia rates at 6 months but not at 12 months with lansoprazole compared to ranitidine could not be contrasted with the different oesophagitis healing rates at 12 weeks as published in the Jaspersen study, the end points were completely different. In view of the fact that symptoms related poorly to efficacy to endoscopic findings in this condition these results were of particular import to prescribers.

The results were therefore not contradictory and the data quoted not a "selective" choice.

Turning to the question of bias raised by the design of the trial, all patients were standardised to the same medicine for healing. This was a standard study design in which all patients were given the same treatment during a run-in period to optimize their clinical condition prior to randomization to study treatment. There was, therefore, no evidence of selection bias. This also reflected the normal practice in Dr Jaspersen's unit where all patients with this condition were treated with 40mg Losec daily for healing. Wyeth's contention was based on the assumption that pre-treatment with Losec during the initial 6-8 week healing phase would make continuation of effect less likely when the patient was switched to another proton pump inhibitor. In view of the fact that all three medicines were efficacious via their action at the proton pump, ie the mechanism of action of these medicines was the same, it was highly unlikely that changing from one medicine to another with such similarity in the mechanism of action would lead to bias in this trial.

If there were concerns that the basic study design could lead to bias, this would have led to the rejection of such a study design from the journal Alimentary Pharmacology and Therapeutics. A similarly designed study had appeared in the New England Journal of Medicine.

The allegation that the randomisation was open was without foundation and was rejected.

Furthermore, if this design were problematic it would not have been used by other investigators in the field. A trial comparing lansoprazole 30mg and omeprazole 20mg had also recently been published, using a lansoprazole healing phase.

Astra therefore refuted any assumption of bias within the study.

Finally, Astra refuted totally the challenge that the Jaspersen data was both misleading and insulting to the medical profession. The data were currently the only prospective investigation specifically involving patients with grade IV oesphagitis and therefore formed an important part of the available literature on this subject; use of the Jaspersen data, therefore, could not be considered selective.

The allegations of breaches of Clauses 7.2, 7.5 and 8.2 were rejected by Astra.

## PANEL RULING

The Panel noted that the heading referred to erosive reflux oesophagitis. The statement beneath the heading referred to complicated reflux oesophagitis and the clinical results featured in the bar chart were in respect of reflux oesophagitis complicated by strictures. In the Panel's view all of the terms used related to generally severe oesophagitis. The Panel did not consider that the use of the different terms was misleading and no breach of Clause 7.2 was ruled.

The Panel noted that the Jaspersen data featured in the detail aid showed that from a group of 10 oesophagitis patients treated with lansoprazole, 20% were healed after 12 weeks' therapy. An earlier paper by Swarbrick *et al* showed that from a group of 78 oesophagitis patients treated with lansoprazole, 70% did not require

redilatation during 12 months' therapy. The Panel accepted that the outcome measures were different but considered that both were relevant to the maintenance of oesophagitis patients. The Panel did not consider that the 20% figure shown in the detail aid represented the balance of the evidence with regard to the efficacy of lansoprazole in oesophagitis patients. A breach of Clause 7.2 of the Code was ruled.

The Panel noted that there was two phases to the Jaspersen study; an initial 8 week healing phase when all patients were treated with omeprazole 40mg daily followed by a four week maintenance phase where patients were randomized to omeprazole, lansoprazole or pantoprazole. The Panel considered that this information should have been given in the description of the study design, not to have done so was misleading. A breach of Clause 7.2 was ruled.

The Panel did not consider that the use of the Jaspersen data disparaged the medical profession as alleged. No breach of Clause 8.2 was ruled.

The Panel noted that the source of the Jaspersen data had been clearly given such that it would be able to be located within the published literature. No breach of Clause 7.5 was ruled.

### APPEAL BY ASTRA

Regarding the Panel's ruling that use of the 20% figure shown in the detail aid did not represent the balance of evidence with regard to the efficacy of lansoprazole in oesophagitis patients and therefore was in breach of Clause 7.2, Astra said that the Panel accepted that the outcome measures used in Jaspersen when compared to Swarbrick were different but did not accept that the 20% healing rate for lansoprazole 60mg from Jaspersen represented the balance of evidence.

The end point in the Jaspersen study provided a very strict and difficult to achieve measure of efficacy. This measure (no oesophagitis, no stricture and no symptoms) provided a global measure of the end points which interested doctors and patients. It included physical healing by absence of oesophagitis and stricture and symptomatic well-being, ie the patient's response.

The symptoms of reflux oesophagitis associated with stricture were heartburn, acid regurgitation, dysphagia and odynophagia. The need for redilatation was a small part of the total management of this condition and the end point 'need for re-dilatation' in the Swarbrick study could not be directly related to the end point 'no oesophagitis, no stricture and no symptoms' in the Jaspersen study. Astra also pointed out that, in the Jaspersen study, only one patient from the lansoprazole group and one patient from the Losec group required re-dilatation. As the two studies had totally different end points, the Swarbrick study was not valid for the assessment of balance of evidence in this case.

Reflux oesophagitis complicated by stricture was an extreme form of reflux oesophagitis. The presence of stricture implied physical damage below the oesophageal mucosa complicated by fibrosis and scarring. As such, it was a difficult condition to manage and treat effectively. Severe reflux oesophagitis appeared to be associated with a slower rate of oesophageal acid clearance than mild reflux oesophagitis. As such it also appeared to be physiologically as well as pathologically different to milder reflux oesophagitis.

The Jaspersen study was the only directly comparative study between proton pump inhibitors in this condition and was the balance of evidence.

Astra therefore appealed against the Panel's ruling of a breach of Clause 7.2.

### APPEAL BOARD RULING

The Appeal Board accepted that the Jaspersen and the Swarbrick studies were very different and that their results could not be compared. The Appeal Board noted, however, that the Jaspersen study presented data from only 30 patients and had only been published as a scientific abstract. The patients involved had complicated reflux oesophagitis and the results for lansoprazole showed that in 10 patients treated with 60mg daily only 20% were healed at 12 weeks. The Appeal Board noted that the Zoton data sheet gave a dose of 30mg for Zoton in gastro oesophageal reflux disease and not 60mg as implied on the page in question. In the Appeal Board's view, given that Zoton was licensed for use in gastro oesophageal reflux disease, the Jaspersen data represented a particular result in a small niche of patients with severe disease. The Appeal Board was concerned that a whole page of the detail aid and a major claim had been based on a scientific abstract reporting results in a small number of patients. The Appeal Board considered that the comparisons made in the detail aid were not sufficiently qualified. The page was not balanced nor fair. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2.

The appeal on this point failed.

## 9 Heading "Losec's efficacy in eradicating *H.pylori* makes it highly cost-efficient"

### COMPLAINT

Wyeth alleged that this page was in breach of Clauses 7.2 and 7.6. The headline was in itself misleading, Losec alone did not eradicate *H. pylori*, it simply provided the right environment for the accompanying antibiotics to eradicate the organism. This was a breach of Clause 7.2.

The main page consisted of two bar charts, the first from an open trial of *H.pylori* eradication with Losec, amoxycillin and metronidazole (OAM) (Bell *et al* (1995). The cost per patient *H.pylori* eradicated was given as £21.71. The second bar chart was taken from a trial looking at lansoprazole with the various licensed antibiotic combinations (Misiewicz *et al* (1996)) with costs per patient of between £23.39 to £30.72. Clearly the doctor was then led to believe that Losec was the cheaper option.

Overall Wyeth suggested that the representation of the data was misleading, the trials were not comparable, and therefore contravened Clauses 7.2 and 7.6.

a) The OAM eradication rates given were not representative of all those available from published studies.

b) It was not apparent what eradication rates were used in the "cost per patient eradicated" calculation.

c) A true assessment of the studies could not be made, essential details were missing:

- No patient numbers were given.
- Was the Bell study multicentre or single centre, comparative or non-comparative, open or closed.
- What statistical analyses had been presented.
- What was the metronidazole resistance like.

d) It was not clear which eradication rate had been used in the OAM regimen, Bell quoted 3 possible rates.

e) Whilst the costings for all the licensed lansoprazole regimens were presented, Astra had presented data for only one omeprazole regimen.

f) The OAM regimen quoted by Astra appeared to be licensed in *H.pylori* positive duodenal ulcer patients. The referenced study (Bell *et al*) quoted patients as having endoscopically confirmed duodenal ulcer, gastric ulcer or non-ulcer dyspepsia. Inclusion of these patients appeared to be outside the terms of Astra's licence.

g) The reference quoted for the lansoprazole regimens (Misiewicz *et al*) also included an OAM arm – this data appeared to have been selectively excluded.

h) Currently available eradication Guidelines from Maastricht and the British Society of Gastroenterology advised that the proton pump inhibitors used in an eradication regimen should be at a bd dose. The Losec example quoted here used a 40mg once daily regimen.

Wyeth was concerned that the selective use of data, as outlined above, was misleading and in breach of Clause 7.2.

## RESPONSE

Astra rejected any breach of Clause 7.2. The headline was intended to direct the reader to the body of the copy where it was made quite obvious that the use of proton pump inhibitors in combination therapy was being discussed.

Astra responded to each one of Wyeth's points as follows:

a) The OAM cost/patient *H.pylori* eradicated was clearly referenced to the Bell study which was a large well-conducted trial in 436 patients with peptic ulcer disease. While not all published studies using this regimen showed eradication rates as high as 91%, the data reinforced the fact that OAM was a highly efficacious method of eradicating *H.pylori* and was a true reflection of the author's findings in a large scale study in this condition.

b) This was clearly stated at the bottom of the page as the cost of the regimen, based on manufacturers' listed prices in MIMS, divided by *H.pylori* eradication rate. The eradication rate used was the gross eradication as quoted in the paper, this eradication rate took into account data from 305 of 308 patients involved. The information was available on request.

c) The Bell publication contained all this information, was readily accessible and available on request. Patient numbers (n=436) were stated in the study description. It was clearly inappropriate to include all the information which described a study within the detail aid. The detail aid as it stood, together with the availability of references on further enquiry, provided sufficient information.

d) The detail aid referred to the gross *H.pylori* eradication rate as previously described. This rate was shown earlier within the body of the detail aid.

e) This was the most widely prescribed regimen, and therefore of the most relevance to UK prescribers. Lansoprazole eradication data was presented on a variety of regimens to avoid allegations of data selection.

f) *De facto*, the Bell trial was a study of *H.pylori* eradication therapies which would not have been appropriate unless the patients with peptic ulcer disease were proven *H.pylori* positive. This was reflected in the paper. As quoted previously, the detail aid used the Bell paper as an illustration of *H.pylori* eradication rates and the cost savings that might accrue with use of Losec. This was reflected in the title "Losec's efficacy in eradicating *H.pylori* makes it highly cost-efficient".

g) The quoted Misiewicz study did not use the recommended licensed doses of antibiotics ie amoxycillin 500mg tds plus metronidazole 400mg tds in combination with omeprazole; the antibiotics were administered twice instead of three times daily and only a total daily dose of 800mg of metronidazole (instead of the recommended 1.2gm) was used. The data from the Misiewicz study were therefore not included for Losec because the regime employed did not reflect the licensed dosage regimen.

h) The Bell study was published before the currently available guidelines. Both 40mg od and 20mg bd were licensed in the eradication of *H.pylori*. The licence drew no distinction between the two. This was entirely consistent with the terms of Astra's licence.

The allegation of breaches of Clause 7.2 and 7.6 by Wyeth were rejected.

## PANEL RULING

The Panel noted that the heading "Losec's efficacy in eradicating *H.pylori* makes it highly cost-efficient" implied that Losec alone eradicated *H.pylori* which was not so. The Panel considered that the heading was misleading and ruled a breach of Clause 7.2 of the Code.

The Panel noted that the cost data for Losec had been calculated according to the eradication rate of 91.1% reported by Bell *et al* (1995) following use of triple therapy with Losec/amoxycillin/metronidazole (OAM) in patients with duodenal ulcers, gastric ulcers and non-ulcer dyspepsia. The Panel noted that OAM therapy was indicated as *H.pylori* eradication therapy only for patients with duodenal ulcers. Figures for the eradication rate only on patients with duodenal ulcer was not available from the paper by Bell *et al*. The Panel considered that to base treatment costs on a specific eradication rate reported in patients other than those for whom OAM therapy was indicated was misleading in breach of Clause 7.2 of the Code.

The Panel considered that its ruling of a breach of Clause

7.2 covered the allegation of a breach of Clause 7.6 and made no ruling in this regard.

The Panel noted that the description of the work by Bell *et al* lacked any details regarding the design of the study. It was a single centre open study. The Panel considered that it would have been helpful to include such details but their omission did not mislead. No breach of Clause 7.2 was ruled.

### APPEAL BY ASTRA

Regarding the Panel's ruling that the heading "Losec's efficacy in eradicating *H.pylori* makes it highly cost efficient" implied that Losec alone eradicated *H.pylori* and that this was misleading and in breach of Clause 7.2, Astra said that the page very clearly presented *H.pylori* eradication in the context of proton pump inhibitors in combination with antibiotics. Text boxes to the left of each bar on the graphs specified which combination regimes were used and abbreviated designations for each regime – OAM and LAM/LCM/LAC – were in clear view on each of the bars.

The headline was also in context with the earlier part of the detail aid (page 7) which presented Losec/antibiotics combination regimens and their *H.pylori* eradication rates. The Panel ruling of no breach on this section took into account that the intended audience would understand the principles of *H.pylori* eradication and combination therapy.

Astra reiterated that the detail aid was for use in front of an expert audience who were well aware of the current management of *H.pylori* disease with combination therapy. The detail aid was tested with hospital physicians to ensure that the layout was clearly understood. Astra therefore appealed against the Panel's ruling of a breach of Clause 7.2.

Regarding the Panel's ruling that the use of the Bell data to base treatment costs on a specific eradication rate reported in patients other than those for whom OAM therapy was indicated was misleading and in breach of Clause 7.2, Astra referred to its previous comments on this matter. Astra therefore appealed against the Panel's ruling of a breach of Clause 7.2.

### APPEAL BOARD RULING

The Appeal Board noted the heading "Losec's efficacy in eradicating *H.pylori* makes it highly cost-efficient". The detail aid had been designed for use with hospital doctors. Given the target audience the Appeal Board did not consider that the heading would mislead readers to assume that Losec monotherapy would eradicate *H.pylori*. The Appeal Board ruled no breach of Clause 7.2.

The appeal on this point was therefore successful.

With regard to the use of the Bell study, to quote a specific cost of omeprazole/metronidazole/ amoxycillin therapy, the Appeal Board referred to its earlier comments on the data (point 7 above). The Appeal Board considered that it was misleading to base the cost of therapy on a specific eradication rate reported in patients other than those for whom OAM therapy was indicated.

The Appeal Board noted that only the cost of one triple therapy with Losec was given, ie OAM therapy. Other triple therapies were indicated for the eradication of *H.pylori*, namely omeprazole/clarithromycin/ metronidazole (OCM) and omeprazole/amoxycillin/ clarithromycin (OAC). For lansoprazole the cost of lansoprazole/amoxycillin/metronidazole (LAM) was given as well as the cost of lansoprazole/clarithromycin/ metronidazole (LCM) and lansoprazole/amoxycillin/ clarithromycin (LAC). The Appeal Board noted that clarithromycin was an expensive antibiotic and to therefore quote prices for LCM and LAC therapy but not OCM or OAC therapy had the effect of making lansoprazole based therapy appear much more expensive than omeprazole based therapy whereas the real cost differential lay with the choice of antibiotics.

Overall, the Appeal Board considered the cost data was misleading and upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal on this point failed.

### 10 Heading "High patient tolerability"

This page featured two bar charts depicting percentage of patients with adverse events. One chart compared Losec after 0-12 months' treatment and 12-24 months' treatment (Joelson *et al* (1992)) while the other compared 12 months' treatment with lansoprazole or ranitidine (Gough *et al* (1996)). The two bar charts were opposite one another and drawn to the same scale.

### COMPLAINT

Wyeth alleged that this page was in breach of Clauses 7.2, 7.5, 7.6 and 7.7. Once again Astra had presented data with the apparent intention of misleading. When all available data was reviewed, it was quite clear that the two products were comparable in terms of their adverse reaction profile. To suggest otherwise was misleading and disparaging.

The bar chart of lansoprazole and ranitidine showed adverse event rates of 48.6% and 34.5% respectively, compared to the 38% and 30% seen with Losec. This was clearly meant to imply that Losec was better tolerated than lansoprazole, and also that 50% of patients on lansoprazole suffered from adverse reactions.

This was not the case and a review of currently available data (Colin-Jones (1993) and Leufkens (1997)) showed quite clearly that the side effect profile of the two products was comparable and at a much lower incidence than was suggested by the graphs.

The graphs also referred to adverse events (the majority of which would not be associated with the medicine) rather than the more usual adverse reactions. Whilst this terminology was not unusual, it was something that not all healthcare professionals were fully conversant with, and no explanation was offered as to the differences in terminology.

Wyeth considered this to be misleading, unbalanced, and disparaging so breaching Clauses 7.2 and 7.7.

The graphical representation of the two trials was also misleading. They were completely different and should

not be made to appear comparative in this way, the layout on the page (side by side) invited comparison, thus breaching Clause 7.6.

The data from the Gough study had also been misrepresented. The lansoprazole group had a higher efficacy rate and therefore stayed on treatment for longer, which of course meant that more adverse events occurred. This was referred to in the paper, and once it was taken into account, there was no difference between lansoprazole and ranitidine. This information was ignored.

Once again Wyeth believed that the intention was to mislead the prescriber into believing that the profile of lansoprazole was worse than both Losec and ranitidine – a further breach of Clause 7.2.

## RESPONSE

Astra said that the information presented described the adverse event profiles of 1) Losec over 0-12 months versus Losec over 12-24 months and 2) lansoprazole over 12 months versus ranitidine over 12 months.

The referencing, with a detailed description of each study on the page, clearly showed that the two separate graphs related to two separate studies. At no stage was a direct comparison drawn between lansoprazole and omeprazole, any implication of comparison by way of format was also rejected.

The graphs clearly stated that it was the adverse event profile which was described in the separate graphs rather than the number of adverse reactions. The graph comparing lansoprazole with ranitidine was true to the data in the reference and stated clearly that 48.6% of the patients involved experienced adverse events in the lansoprazole group.

Astra noted that Wyeth maintained that a review of "the currently available data" showed a comparable and lower adverse event profile for omeprazole and lansoprazole. The data sets for Gough *et al* and Leufkens *et al* were not comparable. In the Leufkens paper only 55.1% of the patients had reflux oesophagitis, a possible source of bias. In 8.5% of patients in the study, lansoprazole was used as part of combination therapy with antibiotics. The short exposure period to lansoprazole (2 weeks or less) in this large subgroup of patients biased to under reporting of adverse events. Despite this bias, the percentage of patients reporting adverse events overall was still relatively high at 19.9% of patients.

Regarding the Colin-Jones paper, this paper reviewed three of the 8000 plus published papers on omeprazole to make claims of comparable safety. This publication (1993) could not be regarded as a "review of the currently available data". Again this review was not indication specific and lacked comparability with the Gough data in the detail aid. Astra, therefore, rejected the allegation that the side effect profile of lansoprazole was misrepresented in the data.

A comparison of adverse event rates between omeprazole and lansoprazole in some of the trials performed with lansoprazole was provided (Hatlebakk *et al* (1993) and (1997); Castell *et al* (1996); Ekström *et al* (1995) and Gough *et al* (1996)), the Gough data being included for comparison.

It was noteworthy that of these comparisons, in a long term chronic condition, the Hatlebakk (1997) paper was comparable to Gough (1996) as both were run over a 12 month period. The adverse event rate in the Hatlebakk study was even higher. Astra contended therefore, that the data was representative of the published literature.

Astra noted that the graphs referred to adverse events and, as Wyeth had pointed out, the terminology was not unusual and was indeed self explanatory. The adverse event profile of a medicine might give a better description than its adverse reaction profile as it prevented allegations of bias resulting in under reporting of side effects not previously thought to be associated with a medicine's effects. Astra rejected the view that there was any need to expand on this further.

On the basis of the above Astra rejected the contention that the presentation of data was misleading, unbalanced and disparaging, and breached Clause 7.2 and 7.7 of the Code. Regarding the alleged breach of Clause 7.6 by the layout used, this was rejected on the grounds of the clear referencing which differentiated the trials in a legible straightforward manner. Astra also noted that at no point on this page was a direct comparison made between the products lansoprazole and omeprazole.

The complainant was correct that the Gough paper showed non significant differences in adverse event rates between the groups. This was reflected in the designation p=ns, clearly seen on the page adjacent to the graph. The information was not ignored.

Astra believed that the layout and design of this page was a fair and accurate representation of the facts by depicting data on two separate studies. Breaches of Clauses 7.2, 7.7 and 7.6 were rejected.

## PANEL RULING

The Panel noted that the two bar charts appeared side-by-side on page 13. Although the colours used for each chart were different the scales were identical thus facilitating direct comparison between the two. The percentage of patients with adverse events with Losec after 0-12 months was 38% and after 12-24 months, 30%. The percentage of patients with adverse events after 12 months' treatment with lansoprazole was 48.6% although the Panel noted that this was not statistically different to the 34.5% reported for ranitidine.

The Panel noted that the results for lansoprazole vs ranitidine had been marked p=ns in small print beneath the bar chart. It was an accepted principle under the Code, however, that misleading impressions could not be qualified by small print. The visual impression given by the bar chart was that the percentage of patients with adverse events was more with lansoprazole than ranitidine which was not so. The two bar charts together gave the impression that the percentage of patients with adverse events on lansoprazole was more than Losec.

The Panel noted that the Losec data had been taken from a study by Joelson (1992) which had included patients with poorly responsive gastric ulcer or reflux oesophagitis. The Gough paper, from which the lansoprazole data had been taken, included only patients with reflux oesophagitis. The papers, therefore, reported

adverse events associated with different disease states. The Panel noted that the Leufkens paper was a 2-year follow-up study of users of lansoprazole and included mostly patients with reflux oesophagitis, gastritis and duodenal ulcers. The authors reported that 80.1% of users reported no adverse events during exposure to lansoprazole. Colin-Jones (1993), in a review of lansoprazole studies reported that lansoprazole was well tolerated with adverse events being infrequent and having a pattern similar to that experienced with ranitidine and omeprazole. A table in the paper showed that the incidence of adverse events for lansoprazole and omeprazole was comparable (26% and 22% of subjects respectively).

The Panel considered that the presentation of the data regarding patient tolerability for Losec and lansoprazole did not represent the balance of the evidence and was misleading. A breach of Clause 7.2 was ruled.

The Panel considered that its ruling of a breach of Clause 7.2 covered the allegations of breaches of Clauses 7.6 and 7.7 and made no rulings in that regard.

The Panel noted that the source of the Joelson data and the Gough data had been clearly given such that it could be found within the published literature. The Panel considered its ruling of no breach of Clause 7.5 of the Code in point 1 above also applied here.

**Complaint received** 12 February 1998

**Case completed** 21 August 1998

---

**CASES AUTH/681/2/98 and AUTH/682/2/98**

# AMGEN v CHUGAI and RHÔNE-POULENC RORER

## Granocyte detail aid

**Amgen made a number of allegations about a detail aid for Granocyte (lenograstim) issued by Chugai and Rhône-Poulenc Rorer. Amgen was the supplier of Neupogen (filgrastim).**

**The description "Human G-CSF" appeared in three places and the word "human" appeared in large type as a shadow beneath the text on one page. Amgen alleged that this was inconsistent with the summary of product characteristics (SPC) as lenograstim was recombinant human G-CSF, not human G-CSF.**

**The Panel noted that the Medicines Control Agency had not objected to the description "Human G-CSF" so long as it was not qualified by any term that would imply it was identical to the human endogenous molecule. The Panel observed that the brand name Granocyte was immediately followed by "lenograstim - rHuG-CSF" followed by the term "Human G-CSF" which appeared prominently in bold. The term was more prominent than the generic description lenograstim – rHuG-CSF which included the prefix "r" to show it was a recombinant product. The Panel considered that the impression created was that lenograstim was human G-CSF and a breach was ruled. Upon appeal by Chugai and Rhône-Poulenc Rorer, the Appeal Board was concerned about the term "Human G-CSF" but considered that as it was used immediately after the brand name and the generic name in material for a specialist audience its use in that context was not misleading. The word "human" appearing as a shadow over which text was printed was not associated with any reference to the fact that Granocyte was a recombinant product. The Appeal Board considered that it created the impression that lenograstim was G-CSF of human origin and upheld the Panel's ruling of a breach of the Code in that regard.**

**Amgen stated that the headline "The role of glycosylation in the efficacy of Granocyte" suggested that arguments would be discussed which demonstrated that glycosylation had a role to play in the efficacy of Granocyte. The text covered three areas referenced to the scientific literature. In Amgen's view, however, the studies referred to did not address the role of glycosylation in the clinical efficacy of Granocyte. Amgen pointed out the statement "Glycosylation has been shown to improve physico-chemical stability and biological potency in vitro. While the significance of this is unclear, stem cell mobilisation studies in healthy volunteers have demonstrated a 25% greater mobilisation of peripheral blood progenitor cells, compared with a non-glycosylated rG-CSF", alleging that it was not accurate, balanced or fair and was not based on an up-to-date evaluation of all the evidence. No evidence had been presented or referenced to demonstrate any clinically relevant difference between glycosylated and non-glycosylated rHuG-CSFs.**

**In the opinion of the Panel, the heading created the impression that glycosylation was a factor in the clinical efficacy of Granocyte. It was misleading in the absence of clinical data and a breach was ruled. The paragraph referred to by Amgen was also ruled in breach because the Panel considered that including data from *in vitro* and volunteer studies within a section detailing clinical indications was misleading. Upon appeal by Chugai and Rhône-Poulenc Rorer, the Appeal Board considered that the heading "The role of glycosylation in the efficacy of Granocyte" gave the impression that glycosylation was a factor in the clinical efficacy of Granocyte. The use of the word efficacy would be taken to mean clinical efficacy. The Appeal Board did not accept the company's submission that the heading merely posed a question for discussion. Given the absence of clinical data to support the claim, the Appeal Board upheld the Panel's ruling of a breach of the Code. The Appeal Board noted that the paragraph in question was part of an introductory section which summarized features discussed in greater depth elsewhere. The Appeal Board did not consider that a reference to data from *in vitro* and volunteer studies within the introductory section was misleading in the circumstances. The paragraph made it clear that its data were *in vitro* and from healthy volunteers and that the significance was unclear. The detail aid was aimed at a specialist audience and further explanation of the data**

was provided. The Appeal Board ruled no breach of the Code in that regard.

Amgen alleged that a paragraph headed "In vitro biological activity" which described the results of a study, was misleading. The study was not a fair comparison of lenograstim and filgrastim. The authors of the study had taken particular trouble to highlight that the process by which the materials had been prepared for the standardization study had affected the activity of those materials and that they might not reflect the biological activity of the original material. Loss of activity was specifically mentioned in relation to filgrastim. None of these statements had been included in the detail aid. The Panel noted that the primary purpose of the study was assessing the suitability of the ampouled preparations to serve as international standards and clinical efficacy had not been a study endpoint. The Panel considered that the relevant section of the detail aid gave the impression that lenograstim had greater biological activity than filgrastim. This impression was reinforced by the first paragraph which stated that recombinant materials of the same mass might not have the same biological activity. The Panel noted the authors' concerns. In the Panel's opinion the detail aid did not fairly reflect the study and a breach of the Code was ruled.

Amgen alleged that a heading "In vivo preclinical studies confirm in vitro results" was not based on an up-to-date evaluation of all the evidence and did not reflect the evidence clearly. The first sentence beneath the heading stated "The biological potency of lenograstim has been compared to that of filgrastim in preclinical studies". The evidence presented was restricted to a single study of rats which supported the assertion that lenograstim was more potent in this *in vivo* model than filgrastim. Amgen referred to other studies and stated that there was data from one species (rat) to suggest increased *in vivo* activity for lenograstim (although the methodology for filgrastim was flawed) and there were two animal studies in mice and monkeys suggesting that both rHuG-CSFs were equally effective. The balance of evidence suggested that lenograstim and filgrastim were equivalent in *in vivo* preclinical studies. The Panel noted that the heading across two pages stated "Potency of Granocyte confirmed in vitro and in vivo". The subheading "In vivo preclinical studies confirm in vitro results" and the introductory paragraph which stated that "The biological potency of lenograstim has been compared with that of filgrastim in preclinical studies" gave the impression that an evaluation of all relevant studies supported this finding. The subsequent paragraphs discussed the results of one study only. References to other studies were not provided. The section as a whole did not fairly reflect all of the relevant evidence. A breach of the Code was ruled. Upon appeal by Chugai and Rhône-Poulenc Rorer, the Appeal Board noted that the four studies referred to were all *in vivo* (animal) studies. No difference between lenograstim and filgrastim had been shown in two studies. Lenograstim had been shown to be more biologically potent than filgrastim in rats. There was no data in patients to confirm what appeared to be differences between the products. The implication was that the differences were established in patients and this was not so. The Appeal Board considered that the heading "In vivo preclinical studies confirm in vitro results", in conjunction with the heading to the double page spread "Potency of Granocyte confirmed in vitro and in vivo", overstated the position. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Amgen alleged that the statement "In this non-randomised series of patients lenograstim 263 micrograms daily (corresponding to some 3 to 5 micrograms/kg) gave equivalent PBPC mobilisation to filgrastim 10 micrograms/kg daily" was not accurate, balanced or fair and might mislead. The purpose of the study from which it was derived was to define parameters which predicted for rapid engraftment after peripheral blood stem cell transplantation, progenitor thresholds, the proportion of patients who achieved these thresholds with a standardized mobilization regimen and the factors that predicted for mobilization efficiency. It was not a randomized, controlled comparison between two mobilization regimens. Use of the data in a promotional piece was misleading. It implied that a lower dose of lenograstim was as effective as a higher dose of filgrastim. This was not supported either by published papers or the SPCs for the two products. The Panel noted that the SPC for lenograstim stated that its recommended daily dose for mobilization of PBPCs after cytotoxic chemotherapy was 150mcg/m$^2$ of patient body surface area which was equivalent to 5mcg/kg. The recommended dose of Neupogen after cytotoxic chemotherapy was also 5mcg/kg. The Panel considered that the statement in question gave the impression that a comparative study had shown that lenograstim 263mcg daily was as effective as filgrastim 10mcg/kg/day for PBPC mobilization. The Panel noted that the study was not designed to compare the two regimens and also noted the SPC dosing regimens. The Panel considered that the statement was misleading and ruled a breach of the Code.

Amgen alleged that the heading "Significantly greater mobilization of CD34+ cells in healthy volunteers" did not reflect the balance of evidence and was misleading. Two studies had been reported and while one supported the claim the other had failed to detect a difference in this respect between lenograstim and filgrastim. Further, using data from healthy volunteers to suggest superiority when this had not been demonstrated in patients was misleading. The Panel considered that the heading was misleading with regard to the data and a breach was ruled. The Panel did not accept that the juxtaposition of patients and healthy volunteer data under the heading for both pages "Efficacy established in trials of PBPC mobilisation" was misleading. Subheadings made it clear which data was from patients and which from healthy volunteers. No breach was ruled in that regard.

Finally, Amgen stated that the claim "Lenograstim was shown to be more potent at mobilising progenitor cells than filgrastim on a weight-for-weight basis" was a conclusion from a study involving healthy volunteers and no practical outcome in terms of patient benefits had been demonstrated. Moreover, at least one study showed no difference in patients with haematological malignancies. No advantage for lenograstim based on weight had been demonstrated. It was not more potent in the clinical setting and therefore the claim was misleading. The supplementary information of the Code stated that "Claims for superior potency in relation to weight are generally meaningless and best avoided unless they can be limited to some practical advantage". The Panel noted that the study stated "In this study lenograstim was more potent than filgrastim on a weight for weight basis in terms of the rise in

**white cell count and the mobilization of GM-CFC". The corresponding statement in the detail aid was "Lenograstim was shown to be more potent at mobilising progenitor cells than filgrastim on a weight-for-weight basis". In the Panel's view the statement in the detail aid was more general than that in the clinical paper. The Panel considered that on balance the statement was not a fair reflection of the findings of the study and a breach of the Code was ruled.**

Amgen Limited made a number of allegations about a detail aid for Granocyte (lenograstim) which bore the names of Chugai Pharma UK Ltd and Rhône-Poulenc Rorer Limited. Chugai submitted a response on behalf of both companies. Amgen was the supplier of Neupogen (filgrastim).

### 1 "Human G-CSF"

#### COMPLAINT

Amgen stated that this appeared on the front cover and on pages 3 and 5. The word "human" appeared as a shadow across page 6.

The summary of product characteristics (SPC) for lenograstim described lenograstim as:

> "A recombinant glycoprotein (rHuG-CSF) equivalent to the Human Granulocyte Colony-Stimulating Factor isolated from CHU-2, a human cell line. Lenograstim is expressed and glycosylated in a mammalian host cell system, Chinese hamster ovary (CHO) cells."

Amgen alleged that the statement "Human G-CSF" was inconsistent with the SPC. Lenograstim was recombinant human G-CSF, not human G-CSF.

In addition, Amgen drew attention to the heading on page 6 of the detail aid; "Lenograstim (rHuG-CSF)" which was followed by the statement "Lenograstim is a recombinant glycoprotein, expressed in Chinese Hamster Ovary (CHO) cells and indistinguishable in its physiochemical, structural and biological properties from naturally occurring Granulocyte Colony Stimulating Factor isolated from the human cell line CHU-2". The statement was referenced to Asano (1991) and Kubota *et al* (1990).

Amgen stated that the description of lenograstim given within the body of the piece was consistent with its SPC. The extrapolation that, because lenograstim was "indistinguishable" from naturally occurring G-CSF, it was human G-CSF, was flawed.

Amgen pointed out that Asano distinguished between natural and recombinant G-CSF. Kubota *et al* noted that "Recombinant hG-CSF produced in mammalian cells is believed to undergo the proper post-translational modifications. However, CHO cells are different from human cells producing the factor naturally." and concluded "... the recombinant hG-CSF is indistinguishable from its natural counterpart." Under the methods of analysis used in this paper it could not be distinguished from natural (human) G-CSF, but it was clearly described as recombinant G-CSF and was not produced by human cells.

Amgen pointed out that the scientific literature was careful to distinguish between naturally occurring human G-CSF and recombinant human G-CSF, of which lenograstim was an example. Human G-CSF implied that the preparation had been purified from human cells. Recombinant human G-CSF was produced from a non-human cell line transfected with the human G-CSF gene.

The SPC for lenograstim was the document relevant to its promotion and reflected the scientific literature. Use of the term "Human G-CSF" was inconsistent with the lenograstim SPC and was therefore in breach of Clause 3.2.

#### RESPONSE

Chugai stated that the Medicines Control Agency (MCA) had specifically authorised the use of the term "Human G-CSF". Following the launch of Granocyte in the UK in 1994, Chugai had a number of discussions with the MCA over the description of lenograstim in relation to the endogenous human molecule. The MCA's understanding of the term "Human G-CSF" was that it described a peptide with the same amino acid sequence as G-CSF to be found in the human species. It was therefore agreed in writing by the MCA (a copy of the letter was supplied) that the descriptor "Human G-CSF" was allowable for lenograstim provided it was not qualified by any term that would imply that the entire molecule was identical to the human, endogenous molecule.

There were two commercially available preparations of G-CSF available in the UK. Lenograstim (Chugai) was constructed from the cDNA prepared from CHU2 a human squamous cell line and expressed in mammalian cells (Chinese hamster ovary cells). Filgrastim (Amgen) was constructed from cDNA prepared from the bladder carcinoma cell line-5637 and expressed in the bacterium *Escherichia coli*. It was important to note that filgrastim had a different structure to both lenograstim and naturally occurring human G-CSF. Lenograstim had the same amino acid sequence and glycosylation site as naturally occurring human G-CSF whereas filgrastim contained an additional N-terminal methionine (and hence 175 amino acids) and it was not glycosylated (Asano (1991)).

Human G-CSF was a glycoprotein with a molecular mass of 20 KD and consisted of 174 amino acids. The molecule was glycosylated at residue threonine 133. The structure of the sugar moiety, which accounted for approximately 4% of the total weight, was *N*-acetyl-neuraminic acid-a (2, 6)(galactose-ß (1, 3))*N*-acetyl galactosamine (Asano (1991)).

In the study by Kubota *et al* (1990) naturally occurring human G-CSF and lenograstim were purified to apparent homogeneity for structural and biological comparison. The amino acid sequence of lenograstim, composed of 174 amino acid residues, was indistinguishable from that of natural human G-CSF. Both forms had a free cysteine 17 and two intramolecular disulphide linkages between cysteine 36 and cysteine 42 and between cysteine 64 and cysteine 74. The O-glycosylation occurred at threonine 133 in both G-CSFs. The biological activities of natural G-CSF and lenograstim were compared *in vitro* in a colony forming assay. The maximal colony number and the slope of the dose response curves were essentially the same for both G-CSFs. *In vivo* experiments in the CPA mouse assay showed a dose dependent increase in

peripheral leucocytes with both G-CSFs indicating that the two factors had almost the same specific activity. Oh-eda *et al* (1990) reported that the sugar moiety of lenograstim was identical to that of natural human G-CSF.

In conclusion, the MCA had allowed the use of the term "Human G-CSF" as a descriptor for a molecule with the same amino acid sequence as G-CSF to be found in the human species. It was established that lenograstim had the same amino acid sequence as naturally occurring human G-CSF. Furthermore, lenograstim was glycosylated at the same residue and with the same sugar moiety as naturally occurring human G-CSF. The biological activity of lenograstim was indistinguishable from its natural counterpart.

## PANEL RULING

The Panel noted that the summary of product characteristics for lenograstim described the medicine as a recombinant glycoprotein (rHuG-CSF) equivalent to the Human Granulocyte Colony-Stimulating Factor isolated from CHU-2, a human cell line.

The Panel noted that the MCA did not object to the description "Human G-CSF" so long as it was not qualified by any term that would imply it was identical to the human endogenous molecule.

The Panel noted that the detail aid would be used with a specialist audience. In the top right-hand corner of pages 1 (front cover), 3 and 5 the brand name Granocyte was immediately followed by "lenograstim - rHuG-CSF" followed by the term "Human G-CSF" which appeared prominently, in bold. The term was more prominent than the generic description of the product, lenograstim - rHuG-CSF, which included the prefix 'r' to denote that it was a recombinant product. On page six the word 'human' appeared in large type as a "shadow" beneath the text. The Panel considered that the impression created by the detail aid was that lenograstim was human G-CSF. This was incorrect and misleading. The Panel therefore ruled a breach of Clause 7.2 of the Code.

The Panel noted that the size of the non-proprietary name of Granocyte, lenograstim, beneath the most prominent display of the brand name on the front cover of the detail aid was not in accordance with Clause 4.2 of the Code. The Panel requested that the companies be advised of its views in this regard.

## APPEAL BY CHUGAI AND RHÔNE-POULENC RORER

Chugai said that in its original submission it had provided written evidence that the Medicines Control Agency (MCA) had specifically allowed the term "Human G-CSF" as a descriptor for lenograstim provided it was not qualified by any term that would imply that the entire molecule was identical to the human, endogenous molecule. This was in order to differentiate it from G-CSF to be found in other species, or containing a different amino acid sequence. This was agreed at a meeting with the MCA where a number of potential descriptors were discussed. The resulting promotional material was submitted to the MCA and no objections were raised. Chugai therefore believed that it had fully complied with the ruling of the MCA and hence the Medicines Act.

Chugai believed that the term "Human G-CSF" as used in the brochure was neither inaccurate nor misleading and therefore not in breach of Clause 7.2 of the Code. As the MCA had stated, the term "Human G-CSF" could be used to describe a peptide which had the same amino acid sequence as G-CSF to be found in the human species. Lenograstim was derived from the mRNA prepared from the human squamous cell line CHU-2. This mRNA was used to create a cDNA library from which the cDNA for human G-CSF was isolated. The mammalian expression system chosen for this cDNA was the Chinese Hamster Ovary (CHO) cell which was suitable for large scale manufacture of proteins. Furthermore the post-translational modification system in mammalian cells (including human cells and CHO cells), such as glycosylation, differed from other expression systems (such as bacteria or yeast). CHO cells processed mammalian proteins in the same way as human cells. Chugai showed in its previous submission that the resulting structure and function of lenograstim was equivalent to human G-CSF. Furthermore it also showed that the amino acid sequence of filgrastim (which was produced in *E. Coli*) differed from that of endogenous human G-CSF in that it possessed an N-terminal methionine amino acid residue.

The demonstrated structure of lenograstim in fact went beyond that required by the MCA definition of human G-CSF. As well as the amino acid sequence being the same as endogenous human G-CSF the glycosylation site and the position of the inter-chain disulphide bonds were also the same. Therefore Chugai submitted that the term "Human G-CSF" was an accurate descriptor of lenograstim as it applied to the final protein product (irrespective of the cell system used for its expression and large scale production) and did not imply that it was produced in human cells.

There were precedents that supported this assertion. For example insulin could be derived from porcine material or be manufactured using recombinant DNA technology. The term "human" was used in the approved trade name of a number of different types of insulin produced by recombinant technology to differentiate them from porcine derived material. The relevant section of the British National Formulary (BNF, No 35, March 1998) was provided together with SPCs for Human Mixtard and Pork Insulatard. The cell line used in the production of human insulin was *E. Coli* ie a bacterial system. The term "human" was used to reflect that the manufactured insulin had the same amino acid sequence as the endogenous human protein and did not imply that the origin of the cells used in manufacture were human.

Chugai thanked the Panel for pointing out the fact that the non-proprietary name of Granocyte (lenograstim) on the front cover of the detail aid was not in accordance with Clause 4.2 of the Code.

## APPEAL BOARD RULING

The Appeal Board noted that Chugai and Rhône-Poulenc Rorer had disputed whether the Panel's ruling of a breach of Clause 7.2 had been appropriate given that Amgen had alleged a breach of Clause 3.2 of the Code. The Panel had considered that Clause 7.2 was the more appropriate

clause. The company stated that it would have answered the allegation differently if it had known that it was to be considered under Clause 7.2 of the Code. The letter of appeal had addressed the issue of a breach of Clause 7.2 and it was agreed for the appeal to be heard in relation to Clause 7.2.

The Appeal Board examined the Granocyte logo which appeared in the top right hand corner of the front cover and pages 3 and 5. "GRANOCYTE" appeared in bold logo type at the top above the phrase "lenograstim - rHuG-CSF". The strapline underneath read "HUMAN G-CSF".

The Appeal Board noted that the company had met with staff from the pharmacovigilance unit of the MCA who had asked that the phrase "Human identical" should not be used. The MCA had agreed that the phrase "Human G-CSF" could be used provided it was not qualified by any term that could imply that the molecule was identical to the human endogenous molecule.

The Appeal Board noted that Chugai had agreed to increase the size of the generic name to meet the requirements of Clause 4.2 of the Code. The Appeal Board was concerned about the use of the term "Human G-CSF" but considered that as it was used immediately after the brand name and the generic name in material to a specialist audience its use in that context on pages 1, 3 and 5 of the detail aid was not misleading.

The Appeal Board examined page 6 of the detail aid on which the word "human" appeared in large type as a "shadow" over which text was printed. The word was not directly associated with any reference to the fact that Granocyte was a recombinant product. The Appeal Board considered that the use of the word "human" created the impression that lenograstim was G-CSF of human origin. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal on this point failed.

**2 "The role of glycosylation in the efficacy of Granocyte"**

**COMPLAINT**

Amgen stated that the use of this headline across the double page spread on pages 6 and 7 suggested that arguments would be discussed which demonstrated that glycosylation had a role to play in the efficacy of Granocyte. The text covered three areas which were referenced to the scientific literature.

Firstly a description of lenograstim and demonstration that in animal models lenograstim had a similar dose response curve to endogenous human G-CSF; secondly evidence that glycosylation of lenograstim protected it against polymerization and denaturation *in vitro*, and suggestions as to how this might be effected; and thirdly evidence that the glycosylated form of rHuG-CSF was more stable *in vitro*. One study was quoted in which a series of assays comparing lenograstim with its de-glycosylated form were conducted and suggested that lenograstim was more stable than de-glycosylated lenograstim *in vitro*. A second study compared lenograstim with *E.coli* derived non-glycosylated rHuG-CSF in an *in vitro* assay.

However, in Amgen's view these studies did not address the role of glycosylation in the clinical efficacy of Granocyte. No evidence was presented to suggest that glycosylated and non-glycosylated rHuG-CSFs had different effects on neutropenia following cytotoxic chemotherapy or that there were any differences in mobilizing autologous peripheral blood progenitor cells (PBPCs) in patients with neoplastic disorders for subsequent re-infusion following high dose chemotherapy.

Amgen alleged that the heading was misleading in breach of Clause 7.2.

Amgen pointed out the following paragraph which appeared on page 6:

> "Glycosylation has been shown to improve physico-chemical stability and biological potency in vitro. While the significance of this is unclear, stem cell mobilisation studies in healthy volunteers have demonstrated a 25% greater mobilisation of peripheral blood progenitor cells, compared with a non-glycosylated rG-CSF."

Amgen alleged this was not an accurate, balanced or fair statement, and it was not based on an up-to-date evaluation of all the evidence. It was potentially misleading because firstly, no evidence had been presented or referenced which demonstrated any clinically relevant difference between glycosylated and non-glycosylated rHuG-CSFs. To Amgen's knowledge, no such evidence existed. Secondly, there was a clear intention to link the studies demonstrating differences in stability and activity in *in vitro* assays to findings in healthy volunteers. Although these were not referenced at this point, Amgen assumed that these findings were taken from the two studies described on page 11 of the brochure. Thirdly, data from healthy volunteers could not be directly extrapolated to patients with neoplastic disorders undergoing PBPC mobilization. The positioning of this information following a paragraph detailing the licensed indications for lenograstim and under a general heading "The role of glycosylation in the efficacy of Granocyte" was liable to mislead as to the significance of the findings. Finally, there was at least one study in the public domain (Kulkarni *et al* (1997)) which demonstrated no significant difference between lenograstim and filgrastim (non-glycosylated rG-CSF) in mobilization of PBPCs in patients with haematologic malignancies.

Information with regard to efficacy of PBPC mobilization in patients (the indication for which the two products were recommended) was the only information relevant to prescriptions for the approved indications.

In addition, using data from the healthy volunteers to suggest superiority when this had not been demonstrated in patients was misleading.

**RESPONSE**

Chugai stated that it believed that there had been no breach of Clause 7.2 of the Code. Pages 6 and 7 discussed the role of glycosylation of G-CSF as determined from *in vitro* and *in vivo* studies.

The supplementary information to Clause 7.2 of the Code

relating to the use of data derived from *in vitro* studies, studies in healthy volunteers and in animals stated that:

> "Care must be taken with the use of such data so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there is data to show that this is of direct relevance and significance."

Chugai noted that Amgen cited an abstract by Kulkarni *et al* (1997) as being in the public domain and demonstrating no significant difference between lenograstim and filgrastim in PBPC mobilization. However this interim report was published in November 1997 and was therefore not available at the time of preparation of the detail aid. Furthermore, this abstract was an interim report of an incomplete study comparing lenograstim with filgrastim in the mobilization of autologous peripheral blood stem cells in patients with haematological malignancies. The abstract stated that it was planned to randomize 80 patients to either 2 (for patients <80kg bodyweight) or 3 (for patients >80kg) vials of lenograstim or a microgram equivalent dose of filgrastim. At the time of publication of this abstract only 28 patients had entered the study (15 randomised to lenograstim and 13 to filgrastim). Therefore it was not yet possible to draw any conclusions from these data.

Chugai stated that it had been careful to ensure that the reader was left in no doubt that these studies were either *in vitro* studies or *in vivo* studies in animals. Paragraph 2 on page 6 of the detail aid clearly stated that the significance of these findings was unclear. Furthermore, the text clearly stated that the results of the quoted PBPC studies applied to healthy volunteers and there was no attempt to extrapolate this data to the clinical situation. Therefore there was no attempt to mislead the reader about the significance of the results.

## PANEL RULING

In the opinion of the Panel the heading created the impression that glycosylation was a factor in the clinical efficacy of Granocyte.

The introductory paragraphs discussed the licensed indications for Granocyte. Subsequent paragraphs discussed the results of *in vitro* and *in vivo* studies and stated that glycosylation had been shown to improve physico-chemical stability and biological potency *in vitro*. No clinical data was presented.

In the opinion of the Panel the heading was misleading given the absence of clinical data. The Panel ruled a breach of Clause 7.2 of the Code.

The Panel examined the paragraph on page 6 of the detail aid which stated that, while the significance of *in vitro* studies demonstrating glycosylation to be associated with improved physico-chemical stability and biological potency was unclear, stem cell mobilization studies in healthy volunteers had demonstrated a benefit for lenograstim in comparison to a non-glycosylated rG-CSF. The Panel noted that this paragraph appeared immediately below, and in the same blue type face, as the introductory paragraphs detailing the clinical indications for Granocyte. The Panel considered that including data from *in vitro* and volunteer studies within a section detailing the clinical indications of lenograstim was misleading. The Panel therefore ruled a breach of Clause 7.2 of the Code.

The Panel noted that the Kulkarni data had been published in November 1997. The data was in the form of an abstract and represented the preliminary results of a study. Data was presented from only 28 out of a planned 80 patients. The Panel considered that such incomplete data should be treated with caution. The failure to refer to Kulkarni *et al* in the detail aid did not mean that the company had failed to reflect all of the relevant evidence. No breach of Clause 7.2 was ruled.

## APPEAL BY CHUGAI AND RHÔNE-POULENC RORER

The Panel had ruled two separate breaches of the Code in this section and Chugai appealed against both of these rulings.

In the first instance the Panel ruled that the heading on pages 6 and 7 "The role of glycosylation in the efficacy of Granocyte" was in breach of Clause 7.2 given the absence of clinical data. Chugai believed that the Panel might have been unduly influenced by the wording of Amgen's complaint with regard to the necessity of clinical data in the evaluation of efficacy.

Chugai submitted that this heading was merely a descriptor of the subsequent discussion of the role of glycosylation in the efficacy of Granocyte and was not claiming a role of glycosylation *per se*. Efficacy was a broad term which was not limited to studies in humans and could therefore also apply to both *in vitro* and *in vivo* studies.

Notwithstanding the above, Chugai also contended that clinical data was not restricted to studies in patients but was a term that could be applied to any studies in human subjects (as in Phase I clinical trials in healthy volunteers). The title of this page did not therefore misrepresent the content of the subsequent pages.

Secondly, the Panel ruled that a paragraph on page 6 of the detail aid was in breach of Clause 7.2 in view of the inclusion of *in vitro* and healthy volunteer data within a section detailing the clinical indications of lenograstim. Chugai did not accept this view as the text of the paragraph clearly stated that the significance of the *in vitro* data was unclear. The use of healthy volunteers in the context of a direct comparison of G-CSF preparations in peripheral blood stem cell mobilization was accepted as the most scientifically appropriate method. This was because it was extremely difficult to obtain a homogenous patient group in this area as there were many factors which influenced the yield of PBPC such as disease type, previous chemotherapy or radiotherapy and the extent of bone marrow involvement by disease. Furthermore the use of healthy volunteers allowed the use of the most appropriate study design for a direct comparison of two compounds, namely a blinded crossover trial which would not be ethical in patients with advanced malignancy. The detail aid would be used with a specialist audience. Chugai submitted that this audience would be fully aware of the above issues and therefore the paragraph was not misleading in any way. Chugai provided a letter from an eminent expert in the field endorsing the views with regard to the use of healthy volunteers.

The company representatives pointed out that the healthy volunteer study data had been accepted by European Authorities as efficacy data for autologous PBPC dossier.

### APPEAL BOARD RULING

The Appeal Board considered that the heading "The role of glycosylation in the efficacy of Granocyte" gave the impression that glycosylation was a factor in the clinical efficacy of Granocyte. The Appeal Board considered that the use of the word efficacy would be taken to mean clinical efficacy. It was assumed that promotional material referred to the clinical situation unless it was clearly stated otherwise.

The Appeal Board did not accept the company's submission that the heading merely posed a question for discussion. Given the absence of clinical data to support the claim the Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal on this point failed.

The Appeal Board noted that the paragraph in question was part of an introductory section which summarized the features discussed in greater depth on pages 6 and 7 of the detail aid. The Appeal Board did not consider that a reference to data from *in vitro* and volunteer studies within the introductory section in the circumstances was misleading. The paragraph made it clear that the data were *in vitro* and from healthy volunteers and that the significance of the data was unclear. The detail aid was aimed at a specialist audience and further explanation of the data was provided on pages 6 and 7. The Appeal Board ruled no breach of Clause 7.2 of the Code.

The appeal on this point was successful.

## 3 "In vitro biological activity"

### COMPLAINT

Amgen stated that the paragraph headed "In vitro biological activity" which appeared on page 8 described results and conclusions from a study by Mire-Sluis *et al* (1995) and the draft report to the Expert Committee on Biological Standardization of the World Health Organisation (WHO) 1994 by Dr Mire-Sluis *et al* based on that study. The objective of this study was to evaluate three ampouled preparations of granulocyte colony stimulating factor for their suitability to serve as international standards for these materials.

Whilst the results and conclusions in the brochure reflected the content of the two papers, use of the study and its report in this way within the context of a promotional item for commercially available lenograstim was misleading and did not present the balance of the evidence to the reader. It was not a fair comparison of lenograstim and filgrastim.

The authors took particular trouble to highlight that the process by which the materials were prepared for the standardization study had affected the activity of those materials and that they might not reflect the biological activity of the original material or material intended for clinical use. Loss of activity was specifically mentioned in relation to the filgrastim preparation.

Specifically, the authors made the following statements:

> "It must be noted that while all efforts were made to retain biological activity after lyophilisation, the ampouled preparations do not necessarily reflect the biological activity of the original material supplied although highly stable activity (suitable for a potency standard) did result."
>
> "It must be noted that the freeze dried preparations used in this study may not exhibit the same biological activity as un-lyophilised preparations or similar materials intended for clinical use or those formulated using different excipients."
>
> "However, the ampouled *E.coli* G-CSF preparation contained less than half the activity of the ampouled CHO G-CSF preparation by bone marrow assay, but it must be noted that the *E.coli* material had lost significant activity during the lyophilisation process."

It was of further note that the G-CSFs were diluted in saline prior to lyophilisation. The SPC for Neupogen (filgrastim) stated that it should not be diluted in saline, whereas diluting lenograstim in saline was recommended in its SPC. Dilution of filgrastim in saline caused the formation of its chloride salt which was insoluble, thus reducing the activity of the preparation.

None of these statements had been included in the material. The reader was left with the impression that filgrastim had a lower biological activity than lenograstim and hence lenograstim was more potent on a weight-for-weight basis. Amgen noted that this finding might have been as a result of reducing the activity of filgrastim by diluting it in saline (filgrastim was not compatible with saline and dilution of filgrastim with saline led to a loss of activity) and loss of activity during the process of lyophilisation of filgrastim, as noted by the authors.

Amgen concluded that using this study to demonstrate biological activity of lenograstim and filgrastim was misleading without a full explanation of the manipulations to which the preparations were subjected and a recognition of the authors' concerns. It was therefore in breach of Clause 7.2.

### RESPONSE

Chugai said that it believed that there had been no breach of Clause 7.2 of the Code.

Chugai noted that Amgen accepted that the conclusion of this paragraph reflected the contents of the quoted two papers.

The paragraph related to an International Collaborative Study co-ordinated by the National Institute for Biological Standards and Control on behalf of the WHO (Mire-Sluis *et al* (1994) and (1995)). The purpose of this paragraph was to point out that biological material of the same mass might have different biological activity. Material for use in this study was provided by Immunex Corporation (USA), Chugai Pharmaceuticals (Japan) and Amgen Inc (USA). Each G-CSF preparation underwent an identical process of preparation for use in this *in vitro* study.

Amgen alleged that the G-CSF preparations were diluted in saline prior to lyophilisation and that this might reduce the activity of the preparation. However this was

unfortunately factually incorrect. Each G-CSF preparation was in fact dissolved in a complex solvent comprising pyrogen free saline containing human serum albumin and trehalose. The addition of human serum albumin would be expected to stabilise the G-CSF and Chugai understood that there was no loss of activity of filgrastim following dissolution in this medium (Mire-Sluis, personal communication). This was further supported by the fact that the mass of filgrastim measured by immunoassay was the same as lenograstim arguing against any significant precipitation of filgrastim as an insoluble chloride. If Amgen continued in its belief that filgrastim was prepared incorrectly for this study, then Chugai suggested that it open a scientific dialogue with the author of the WHO study publication.

The title of this paragraph ("in vitro biological activity") made it clear that this was an *in vitro* study. The limitations of *in vitro* studies were well recognised and no attempt was made to extrapolate these *in vitro* data to the clinical situation. Therefore there was no attempt to mislead as to the significance of these data. Both the text and the figures were clearly referenced (four times) allowing readers to make their own judgement about the data.

**PANEL RULING**

The Panel noted that the section headed "In vitro biological activity" discussed the results of a study by Mire-Sluis *et al* (1995) and a WHO report based upon the results of the study (the Panel had been provided with the draft report to participants). The primary purpose of the Mire-Sluis study was to assess the suitability of the ampouled preparations to serve as international standards for the bioassay and immunoassay of G-CSF and *inter alia* to assay the G-CSF content of the ampoule preparations. The Panel noted that clinical efficacy was not a study endpoint.

Twenty-nine laboratories in eleven countries contributed data to the study. Each participant was asked to carry out at least two independent assays on all of the preparations to be tested. The participants used cell-line assays, bone marrow assays and immunoassays. One laboratory used a receptor-affinity assay. The different assay methods provided different estimates of the relative activity of filgrastim to lenograstim for an equivalent mass of G-CSF. Bioassay showed that filgrastim had a biological potency of half to a third of lenograstim, immunoassay showed that estimated levels of potency were almost identical and bone marrow assay showed that filgrastim had less than half the activity of lenograstim.

The Mire-Sluis study stated that bone marrow assays were more variable in their estimates of potency. Cell line bioassays and immunoassays were similar. Local standards used by the participants in the study showed substantial variation in terms of their origin and calibration. The WHO report stated that due to the difficulty in interpreting the various undefined unitages assigned by the participants, estimates of potency relative to the study preparations were unreliable.

The WHO report stated that the significant differences between the activities of the preparations appeared to be related to differences between the cells used for their biosynthesis although some of these differences might also be the result of different purification methods and of inter batch variations.

The Panel noted that Mire-Sluis *et al* (1995) stated that each preparation of recombinant rHG-CSF was disolved in pyrogen-free saline (0.9% NaCl) containing human serum albumin and trehalose. The resultant solution was distributed into ampoules and lyophilised. The authors noted that the *E.coli* material (filgrastim) had lost significant activity during the lyophilisation process.

The Panel noted that the Granocyte SPC referred to diluting Granocyte in sodium chloride injection. At a particular dilution this would be stable for 24 hours. The SPC for Neupogen (filgrastim) stated that it should not be diluted with saline solution but could be diluted with 5% glucose solution. Dilution to a final concentration less than 2mcg per ml was not recommended at any time.

The Panel noted this was a complex area. Filgrastim did not appear to have been diluted in accordance with the Neupogen SPC which stated that it may be diluted in 5% glucose and that it should not be diluted with saline solutions. The Panel noted the submission from Chugai that human serum albumin would stabilise filgrastim and that the mass of G-CSF was equivalent to that in lenograstim after lyophilisation.

The Panel considered that the relevant section of the detail aid gave the impression that lenograstim had greater biological activity than filgrastim. This impression was reinforced by the final paragraph which stated that recombinant materials of the same mass may not have the same biological activity. The Panel noted the authors' concerns referred to by Amgen. In the opinion of the Panel the detail aid did not fairly reflect the referenced study and the WHO report. The Panel ruled that the detail aid was misleading in breach of Clause 7.2 of the Code.

**4 "In vivo preclinical studies confirm in vitro results"**

**COMPLAINT**

Amgen stated that this heading, which appeared on page 9, was not based on an up-to-date evaluation of the evidence and did not reflect the evidence clearly.

The first sentence beneath the heading stated:

> "The biological potency of lenograstim has been compared with that of filgrastim in preclinical studies."

The evidence presented was restricted to a single study of rats (Wells (1996)). This study supported the assertion that lenograstim was more potent in this *in vivo* model than filgrastim.

However a literature search revealed that there were four pre-clinical studies comparing lenograstim with filgrastim: Wells (1996) (which had also appeared as an abstract by Plard *et al* (1995)), Nohynek *et al* (1997), Shibuya *et al* (1995) and Tanaka *et al* (1997).

Amgen noted that in the two published studies from Wells using rats both had presented the results of a comparison of lenograstim, filgrastim and vehicle at

different doses in groups of eight normal male rats (ie the same experiment was reported twice). The results indicated that the absolute neutrophil counts (ANCs) obtained on days 2, 3 and 5 in the lenograstim treated groups were higher (statistically significant on day 3 at 30 and 100mcg/kg and on day 5 at 10, 30 and 100mcg/kg) than the respective values obtained in the filgrastim treated groups. The conclusion from this comparison was that lenograstim, the glycosylated form of rHuG-CSF, had a greater *in vivo* potency than filgrastim, the non-glycosylated form of the molecule.

Amgen stated that the second study, (Nohynek (1997)), also considered the effects of filgrastim, lenograstim (30mcg/kg/day and 100mcg/kg/day) or vehicle in neutropenic male rats. The authors reported that the ANC values obtained in the lenograstim treated groups were statistically significantly higher on day 3 (30mcg/kg groups) and on days 6 and 8 (100mcg/kg groups). The same conclusion as in the first paper was reached, extending this to neutropenic as well as normal rats. However, on careful examination of the full paper it was noted that the filgrastim used in this study was diluted with 0.9% sodium chloride for subcutaneous injection. Amgen stated that it was well documented that filgrastim was incompatible with saline. This was noted in the SPC for Neupogen (filgrastim). Dilution of filgrastim with saline resulted in the formation of the chloride salt of filgrastim which was insoluble. This would affect the activity of the preparation and might account for the results obtained. In contrast, lenograstim was stable in saline solution and the SPC recommended dilution in saline when required. By treating both preparations with saline solution, filgrastim was affected adversely whereas lenograstim was not affected. Hence the results of these studies must be questioned in the light of methodology inappropriate to filgrastim.

Amgen noted that the study by Shibuya *et al* (1995) had investigated the effects of 3 types of rHuG-CSFs [non-glycosylated; filgrastim, glycosylated; lenograstim and N-terminal mutated; nartograstim] on neutrophil recovery after chemotherapy in a mouse model. The rHuG-CSFs (at 3 or 10mcg/kg) or vehicle were administered and all three rHuG-CSFs showed almost equivalent effect on recovery from neutropenia. The authors concluded: "These results suggest that glycosylation and N-terminal mutation in rhG-CSF have no influence on *in vivo* biological activity."

In a study in cynomolgus monkeys, Tanaka *et al* (1997) also compared the 3 types of commercially available rHuG-CSFs. Daily doses were in accordance with the clinical use of rHuG-CSFs (1.5mcg/kg and 5mcg/kg). Each rHuG-CSF shared similar effects and the peak neutrophil counts were almost identical. "After subcutaneous injection, lenograstim showed relatively lower serum concentrations but a comparison of neutrophil counts showed no corresponding difference between filgrastim, lenograstim and nartograstim". The authors concluded: "The three CSF products used in our investigation were almost equivalent in terms of neutrophil increasing effects. This suggests that neither glycosylation nor the N-terminal mutation in rhG-CSF affected the in vivo effect of neutrophil proliferation which is the principal pharmacologic activity of CSF."

Amgen stated that there was therefore data from one species (rat) to suggest increased *in vivo* activity for lenograstim (although the methodology in relation to filgrastim was flawed) and there were two animal studies in mice and monkeys suggesting that both rHuG-CSFs were equally effective. The balance of evidence suggested that lenograstim and filgrastim were equivalent in *in vivo* preclinical studies. The statement in the detail aid was, therefore, in breach of Clause 7.2.

**RESPONSE**

Chugai believed that there had been no breach of Clause 7.2 of the Code. Chugai noted that Amgen agreed that the text of this paragraph supported the assertion that lenograstim was more potent than filgrastim in this animal model.

There were four published pre-clinical studies comparing lenograstim with filgrastim. Two studies supported the assertion that lenograstim was more potent than filgrastim in animal models and two studies apparently showed no difference. There were no published reports to Chugai's knowledge where filgrastim had been demonstrated to be more potent than lenograstim. Chugai was therefore confused as to how Amgen could consider that the balance of the evidence was not in favour of lenograstim.

Amgen had again alleged that in the study published by Nohynek *et al* (1997) filgrastim was prepared using saline as a diluent. Again this was factually incorrect as the solution for injection also contained 0.1% human serum albumin and, as described previously, it was most unlikely that this would have resulted in reduced activity of filgrastim by formation of an insoluble chloride.

**PANEL RULING**

The Panel noted that Wells (1996) and Plard *et al* (1995), which were in effect the same study, concluded that in a rat model the biological potency of lenograstim was superior to non glycosylated filgrastim. The products had been diluted in 0.9% saline containing 0.1% human serum albumin. Nohynek *et al* (1997) concluded that lenograstim had superior *in vivo* potency in normal and neutropenic animals to non-glycosylated filgrastim. Filgrastim was diluted with aqueous sodium chloride contrary to the recommendation in its SPC.

In Shibuya *et al* (1995), a study in neutropenic mice, and Tanaka *et al* (1997), a study in normal monkeys, filgrastim and lenograstim demonstrated almost equivalent potency. Shibuya and Tanaka both concluded that the results of their studies suggested that glycosylation did not affect the *in vivo* effect of neutophil proliferation. Tanaka *et al* stated that a reason for the discrepency between *in vivo* and *in vitro* results was that *in vivo* efficacy was related to *in vivo* stability, not *in vitro* stability and protease degradation in plasma, thought to be prevented by glycosylation was not a major metabolic pathway of rHuG-CSF.

The Panel noted the heading at the top of pages 8 and 9 stated "Potency of Granocyte confirmed in vitro and in vivo". The subheading "In vivo preclinical studies confirm in vitro results" and the introductory paragraph

which stated that "The biological potency of lenograstim has been compared with that of filgrastim in preclinical studies" gave the impression that an evaluation of all relevant studies supported this finding. The subsequent paragraphs discussed the results of one study only, Wells (1996). References to other studies were not provided. Whilst the text fairly reflected the outcome of Wells (1996) in rats, the section as a whole did not fairly reflect all of the relevant evidence. A breach of Clause 7.2 was ruled.

### APPEAL BY CHUGAI AND RHÔNE-POULENC RORER

Chugai disagreed with the Panel's view that the section did not reflect a balanced view of the available evidence as it believed that the balance of available evidence, based on four studies, was in favour of lenograstim. Two of these publications (Wells (1996) and Nohynek *et al* (1997)) supported the fact that lenograstim was more biologically potent than filgrastim and two publications (Shibuya *et al* (1995) and Tanaka *et al* (1997)) apparently showed no difference between the preparations. There were no publications to Chugai's knowledge that showed superiority of filgrastim over lenograstim. Therefore the balance of evidence was in favour of lenograstim. Amgen had alleged that the publications in support of lenograstim were methodologically flawed as filgrastim was diluted in 0.9% saline which was not in accordance with the filgrastim SPC. This view appeared to have been accepted by the Panel. However, as Chugai stated in its original submission, filgrastim was not diluted in 0.9% saline but in 0.9% saline containing 0.1% human serum albumin. The addition of albumin to protein solutions was a common method of stabilising protein solutions. The relevant section from the "Handbook of Pharmaceutical Excipients" was provided.

Chugai had contacted the study director of the study published by Nohynek who had made the following observations:

1 It was traditional to use saline rather than glucose in rat experiments as this decreased the risk of infection at the injection site.

2 The dilution of both lenograstim and filgrastim was made extemporaneously (time between dilution and injection was less than 30 minutes). This time was too short for inducing any degradation of filgrastim.

3 The addition of human serum albumin (0.1%, 1mg/ml) would not strictly be required at concentrations above 15mcg/ml (the concentration in the study was 83.3mcg/ml). However human serum albumin was added as a precaution and would be sufficient to protect filgrastim from degradation by stabilising the hydrophobic amino acid residues.

4 The dilution in saline was only 1 in 20. In these conditions the protective effect of the excipients contained in the filgrastim formulation (polysorbate 80, mannitol and sodium acetate) was probably still maintained. This was a different situation when compared to the dilution of 1 in 250 or 1 in 500 that was used in clinical practice.

Furthermore both this study and the study by Wells (as used in the Granocyte detail aid) were published in peer reviewed journals and hence the study methodology was accepted by the journals as appropriate.

Finally although Chugai accepted that the European and United States filgrastim SPCs warned against dilution in saline, the Japanese filgrastim package insert specifically allowed for dilution in saline. It would therefore seem that the warning regarding dilution in saline was by no means absolute. Chugai provided a copy of this insert which appeared in the "Japan Pharmaceutical Reference". This publication was supervised by the Pharmaceutical Affairs Bureau of the Japanese Ministry of Health and Welfare.

Chugai therefore contended that the two studies in favour of lenograstim were not methodologically flawed. The weight of evidence was therefore clearly in favour of lenograstim and therefore the text did reflect a considered balance of the available evidence.

### APPEAL BOARD RULING

The Appeal Board noted Chugai's submission that in Japan the package insert for the formulation of filgrastim available there stated that the product could be diluted in saline. Chugai accepted that European and American SPCs/package inserts for filgrastim products stated that they should not be diluted in saline. The Appeal Board noted that the four studies were all *in vivo* (animal) studies. No difference between lenograstim and filgrastim had been shown in two studies. Lenograstim had been shown to be more biologically potent than filgrastim in rats. The data referred to potency. There was no data in patients to confirm what appeared to be differences between the products. The implication was that the differences were established in patients and this was not so. The Appeal Board considered that the heading "In vivo preclinical studies confirm in vitro results" in conjunction with the heading to the double page spread "Potency of Granocyte confirmed in vitro and in vivo" overstated the position. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal on this point failed.

## 5 "In this non-randomised series of patients lenograstim 263 micrograms daily (corresponding to some 3 to 5 micrograms/kg) gave equivalent PBPC mobilisation to filgrastim 10 micrograms/kg daily"

### COMPLAINT

Amgen alleged that this statement, which appeared on page 10, was not accurate, balanced or fair and might mislead. The statement was derived from a study by Watts *et al* (1997a).

The purpose of this study was to define parameters that predicted for rapid engraftment after peripheral blood stem cell (PBSC) transplantation, progenitor thresholds, the proportion of patients who achieved these thresholds with a standardised mobilization regimen and the factors that predicted for mobilization efficiency. It was a non-randomised, uncontrolled, non-blinded series of 101 consecutive lymphoma patients in which the relationship between the number of progenitor cells collected and patient age, sex, diagnosis, prior radiotherapy and time

since last chemotherapy was determined by multivariate analysis. The method of PBPC collection evolved during the programme. For example the timing of the harvest and the number of aphereses performed were altered. These affected yields of progenitor cells. Hence, it could be seen that this study was not a randomised, controlled comparison between two mobilization regimens.

Amgen stated that the authors referred once only to the different mobilization regimens:

> "In initial studies on the mobilization achieved with these two different G-CSF regimens, the kinetics and magnitude of the mobilization were found to be similar. The total numbers of MNC [mononuclear cells], GM-CFC [granulocyte-monocyte-colony-forming cells] and CD34+ cells collected on the first day that the WBC [white blood cell] count was greater than 5.0 x $10^9$/L after the cyclophosphamide nadir were also similar."

In subsequent analyses, the two G-CSF regimens were analysed together.

Amgen alleged that the statement in the detail aid "In this non-randomised series of patients lenograstim 263 micrograms daily (corresponding to some 3 to 5 micrograms/kg) gave equivalent PBPC mobilisation to filgrastim 10 micrograms/kg daily" was misleading. The study was neither designed to compare these regimens nor powered to detect a difference. Failure to demonstrate a difference in such a study was insufficient evidence to suggest equivalence.

Amgen stated that the recommended doses for PBPC mobilization in patients undergoing myelosuppressive or myeloablative chemotherapy for both products were the same, ie 5mcg/kg/day when used alone. The Granocyte SPC stated that the recommended dose of Granocyte of 150mcg per $m^2$ daily was therapeutically equivalent to 5mcg/kg daily as used in clinical studies.

In Amgen's view the terms "similar" (as used by the authors) and "equivalent" (as used in the detail aid) were not synonymous in the scientific context. Use of the word "equivalent" gave a greater emphasis to the findings. Insertion of the comment "corresponding to some 3 to 5 micrograms/kg" was misleading as the conversion from 263mcg per day to a mcg/kg dose was not referred to in the paper. The authors did not provide any information from which this could be calculated.

Use of this data in a promotional piece for lenograstim was misleading. It implied that a lower dose of lenograstim was as effective as a higher dose of filgrastim for mobilization of PBPCs in the context of a piece which aimed to demonstrate superior *in vitro* and *in vivo* potency for lenograstim as well as superior PBPC mobilization in healthy volunteers. This was not supported either by published papers or the SPCs of the two products.

## RESPONSE

Chugai believed that there had been no breach of Clause 7.2 of the Code. This paragraph described the results from a study by Watts *et al* (1997a) which analysed the factors that predicted rapid engraftment after peripheral blood stem cell (PBSC) transplantation, progenitor thresholds, the proportion of patients who achieved these thresholds with a standardized mobilization regimen and the factors that predicted for mobilization efficacy.

The study referred to 101 patients with relapsed or resistant lymphoma who were entered on to the high dose therapy programme. Two regimens were used for peripheral blood stem cell mobilization: cyclophosphamide 1.5g/$m^2$ followed by filgrastim 10mcg/kg daily (43 patients) or cyclophosphamide 1.5g/$m^2$ followed by lenograstim 263mcg daily (58 patients).

Chugai noted that Amgen had alleged that the authors only referred to the different mobilization regimens once in the paper. This was factually incorrect as the authors actually referred twice to the different rHuG-CSF regimens in the paper as detailed below.

a) Impact of rHuG-CSF regimen and leukapheresis machine on PBSC yields

The authors described the results of using two different rHuG-CSF regimens in the mobilization of peripheral blood stem cells. The results were presented in the text and graphically. There was no statistically significant difference between the progenitor cell yield with either rHuG-CSF regimen.

Because of the similarity of the results the authors commented that "in subsequent analyses, the two G-CSF regimens have therefore been analysed together".

b) Factors that predict for PBSC yield

The authors described the multivariate analysis that was performed, the aim of which was to determine which factors predicted for obtaining the various GM-CFC thresholds on a single apheresis collected on the first day the mobilization recovery white blood cell count was greater than 5 x $10^9$/L. The factors considered were age, sex, diagnosis, cycles of previous therapy, previous treatment with radiotherapy, intermittent versus continuous flow apheresis and the rHuG-CSF mobilization regimen used. Previous radiotherapy was the only factor predicting a poor yield on a single apheresis of GM-CFC. The multivariate analysis was also performed for CD34+ yield which gave the same results. Therefore this was further confirmation that the two rHuG-CSF regimens were statistically equivalent in terms of stem cell mobilization.

The statement "corresponding to 3 to 5 micrograms/kg" did not appear in the reference but it had been used a number of times by Professor D C Linch (a co-author of the Watts paper) when he had presented the data from this paper at scientific meetings and conferences (eg British Society of Haematology, 1996 Satellite Symposium "Peripheral Blood Stem Cell Transplantation: The Future").

Chugai had been careful not to mislead the reader with regard to the results of this study. The paragraph of text in the brochure clearly stated that the study was non-randomised. The terms "similar" and "equivalent" were both used in this paragraph qualifying the use of the word equivalent. Furthermore the Collins English Dictionary stated that the word "equivalent" could be defined as "having the same or similar effect or meaning".

**PANEL RULING**

The Panel noted the banner headline across two pages of the detail aid read "Efficacy established in trials of PBPC mobilisation". The relevant section was subtitled "PBPC mobilisation in lymphoma patients" and discussed the results of the Watts *et al* (1997a) study. The aim of the study was to define parameters that predict for rapid engraftment after peripheral blood stem cell (PBSC) transplantation, progenitor thresholds, the proportion of patients who achieve these thresholds with a standardized mobilization regimen and the factors that predict for mobilization efficiency. Patients were mobilized with low-dose cyclophosphamide ($1.5g/m^2$) followed by 10mcg/kg of filgrastim or a single vial (263mcg) of lenograstim.

The Panel noted that the SPC for lenograstim stated that its recommended daily dose for mobilization of PBPCs was $150mcg/m^2$ of patient body surface area which was therapeutically equivalent to 5mcg/kg. The Panel noted that the recommended dose of Neupogen for PBPC mobilization when used alone was 10mcg/kg. The recommended dose for PBPC mobilisation after myelosuppressive chemotherapy was 5mcg/kg.

The Panel considered that the statement in question gave the impression that a comparative study had shown that lenograstim 263mcg daily was as effective as filgrastim 10mcg/kg/day for PBPC mobilization. The Panel noted that the study was not designed to compare the two regimens. It also noted the SPC dosing regimens. The Panel considered that the statement was misleading and ruled a breach of Clause 7.2 of the Code.

## 6 "Significantly greater mobilization of CD34+ cells in healthy volunteers"

**COMPLAINT**

Amgen alleged that this heading which appeared on page 11 did not reflect the balance of evidence, and was misleading.

Amgen stated that two studies had been reported which investigated the mobilization of PBPCs in healthy volunteers using lenograstim and filgrastim, Höglund *et al* (1995) and Watts *et al* (1997b). The Höglund study supported the claim of greater mobilization of CD34+ cells in healthy volunteers, whereas the Watts study failed to detect a difference in the CD34+ cells mobilized by lenograstim and filgrastim. The balance of evidence did not support a claim of significantly greater mobilization of CD34+ cells in healthy volunteers. Therefore Clause 7.2 had been breached.

Amgen also alleged that the statement was misleading in the context of the promotional piece.

Amgen noted that pages 10 and 11 were entitled "Efficacy established in trials of PBPC mobilisation". On page 10, the use of Granocyte in its licensed indication of autologous PBPC mobilization was discussed. Under the same banner headline, healthy volunteer data was presented with a claim for superior mobilization of peripheral blood progenitor cells by lenograstim. Juxtaposition of these two topics, together with the interpretation of the lymphoma patient data (referred to in point 5 above), could mislead the reader with regard to the efficacy of filgrastim for PBPC mobilization.

Amgen stated that Watts *et al* commented thus on the clinical significance of their findings in healthy volunteers, which they believed was limited:

> "The difference in potency observed by Höglund *et al* (1995) and ourselves is small in terms of progenitor mobilization and would only be of clinical relevance in patients with relatively poor mobilization whose collections are borderline for progenitor threshold requirements."

Amgen was not aware of any controlled studies in patients with malignant disease which demonstrated superiority for either lenograstim or filgrastim in relation to mobilization of PBPCs. There was one study in the public domain which indicated that there was no difference in the mobilization capacity of equivalent (mcg/kg) doses of lenograstim and filgrastim (Höglund *et al* (1995)). (Amgen referenced this statement to the Höglund *et al* (1995) study. This study was carried out on 32 healthy volunteers and concluded that lenograstim gave a better mobilization of PBPC compared to an identical dose of filgrastim. It appeared to the Panel that Amgen might have made an error in referencing the statement to the Höglund study.)

Amgen referred to the study by Kulkarni *et al* (1997) which had reported on 28 patients randomised to either lenograstim or filgrastim for mobilization. No statistical difference was seen for MNC, CD34+ or CFU-GM levels between the lenograstim and filgrastim groups. The patient numbers reported in this study were of similar magnitude to those in the Höglund and Watts papers, although it did not have a cross-over design. Kulkarni *et al* concluded: "These preliminary results suggest that a reduced dose of filgrastim or lenograstim is associated with comparable stem cell collections."

Information with regard to efficiency of PBPC mobilization in patients was the only information relevant to prescriptions for the approved medicines. In addition, using data from healthy volunteers to suggest superiority when this had not been demonstrated in patients was misleading.

**RESPONSE**

Chugai believed that there had been no breach of Clause 7.2 of the Code. Chugai was not aware of any studies that demonstrated superior potency of filgrastim in the mobilization of peripheral blood stem cells compared to lenograstim in either healthy volunteers or patients. The results of two studies in healthy volunteers were presented in the text, both of which showed an advantage for lenograstim in terms of peripheral blood stem cell mobilization. The balance of the evidence was therefore that lenograstim was more potent than filgrastim in mobilizing peripheral blood stem cells in this setting.

The study by Höglund *et al* (1995) showed a statistically significant increase in the number of CD34+ cells mobilized at a dose of 10mcg/kg/day of lenograstim as compared with 10mcg/kg/day of filgrastim in healthy volunteers. The study also showed a statistically significant increase in CFU-GM (this term was

interchangeable with GM-CFC) mobilized by lenograstim as compared to filgrastim (14.6 ±1.6 vs 10.3 ±0.9, p=0.0014) although this was not mentioned in the detail aid.

The study in the next column by Watts *et al* (1997b) compared lenograstim with filgrastim at a dose of 5mcg/kg/day in the mobilization of PBPC in healthy volunteers. This column of text was clearly separate from the previous column describing the Höglund study. The text was an accurate reflection of the content of the paper. There was no suggestion that this study demonstrated greater CD34+ mobilization with lenograstim but a significantly greater number of GM-CFC were mobilized with this regime. In fact the mean peak of CD34+ cells was 12% higher with lenograstim but the difference was not statistically significant. The authors commented in the discussion that this might be because a slide based immunoassay was used in this study to assess CD34+ cell numbers rather than the more precise flow cytometry method where a larger number of cells were counted. An alternative explanation was that lower doses of G-CSF might preferentially mobilize more primitive cells as CD34+ cells were on average more mature than GM-CFC.

The study by Höglund *et al* (1995) was submitted to, and accepted as efficacy data by the MCA when the licence for autologous PBPC mobilization was obtained.

Chugai noted that Amgen again cited the abstract by Kulkarni *et al* (1997) as being in the public domain and demonstrating no significant difference between lenograstim and filgrastim in peripheral blood progenitor cell mobilization. Chugai re-iterated that this interim report was published in November 1997 and was therefore not available at the time of preparation of the detail aid. Furthermore this abstract was an interim report of an incomplete study comparing lenograstim with filgrastim in the mobilization of autologous peripheral blood stem cells in patients with haematologic malignancies. The abstract stated that it was planned to randomise 80 patients to either 2 (for patients ≤80kg) or 3 (for patients >80kg) vials of lenograstim or a microgram equivalent dose of filgrastim. At the time of publication of this abstract only 28 patients had entered the study (15 randomised to lenograstim and 13 to filgrastim). Therefore it was not yet possible to draw any conclusions from these data.

The two studies in healthy volunteers were clearly labelled as such and there was no attempt to extrapolate these results to the clinical situation. Therefore there was no attempt to mislead as to the significance of these results.

**PANEL RULING**

The Panel noted that beneath the heading "Significantly greater mobilisation of CD34+ cells in healthy volunteers" was a column of text describing the Höglund data, an adjacent column of text presented the Watts data. The Panel considered that the heading applied to both columns. Two bar charts appeared at the base of each column of text both of which showed statistically significant results in favour of lenograstim. The results depicted from the Höglund data referred to CD34+ cell counts and were clearly related to the heading. The statistically significant results shown from the Watts study referred to mean CFU counts and not CD34+ cell counts. The Panel noted that while Watts *et al* had reported a trend in favour of lenograstim compared to filgrastim in terms of CD34+ cell counts the difference between the two products did not reach statistical significance. The Panel considered that the heading was misleading with regard to the Watts data and the related bar chart. A breach of Clause 7.2 was ruled.

The Panel did not accept that in the circumstances the juxtaposition of patient and healthy volunteer data, under the heading for both pages "Efficacy established in trials of PBPC mobilisation", was misleading. Sub headings made it clear which data was from patients and which was from healthy volunteers. The Höglund *et al* paper had been accepted by the MCA as efficacy data. The Panel ruled no breach of Clause 7.2.

The Panel considered that its comments upon the Kulkarni paper at point 2 above applied here.

## 7 "Lenograstim was shown to be more potent at mobilising progenitor cells than filgrastim on a weight-for-weight basis"

**COMPLAINT**

Amgen said that this claim, which appeared on page 11, was a conclusion from the study by Watts *et al* (1997b) which compared lenograstim and filgrastim for mobilization of PBPCs in healthy volunteers. As the data was derived from healthy volunteers, no practical outcome in terms of patient benefits (for example improved engraftment or fewer aphereses) had been demonstrated. Moreover, there was at least one study (Kulkarni *et al* (1997)) which showed no difference in mobilization of progenitor cells between equivalent doses of lenograstim and filgrastim in patients with haematological malignancies. This study countered the claim that lenograstim was more potent at mobilizing progenitor cells than filgrastim on a weight for weight basis.

Amgen considered that another possible patient benefit of the lenograstim claim could be mobilization with a lower dose of lenograstim than filgrastim. However, the SPCs for lenograstim and Neupogen (filgrastim) recommended the same dose for mobilising PBPCs.

- With chemotherapy:
  Filgrastim 5mcg/kg
  Lenograstim 150mcg/m² – The SPC for lenograstim clearly stated that the recommended dose of 150mcg/m² was therapeutically equivalent to 5mcg/kg as used in clinical studies.

- Alone:
  Filgrastim 10mcg/kg
  Lenograstim 10mcg/kg

No advantage for lenograstim based on weight had been demonstrated to the regulatory authorities, and promotion must be in accordance with the marketing authorization for the product. Lenograstim was not more potent in the clinical setting and therefore the claim was misleading.

A breach of Clause 7.2 was alleged. The supplementary

information to Clause 7.2 stated: "Claims for superior potency in relation to weight are generally meaningless and best avoided unless they can be linked to some practical advantage."

## RESPONSE

Chugai believed there had been no breach of Clause 7.2 of the Code. This statement was from the conclusion of the paper by Watts *et al* (1997b). It was clearly linked to this study in healthy volunteers in the text of the brochure and no extrapolation to patients was made. Therefore there was no attempt to mislead in this regard.

Chugai noted that Amgen again cited the abstract by Kulkarni *et al* (1997) as being in the public domain and demonstrating no significant difference between lenograstim and filgrastim in peripheral blood progenitor cell mobilization. However Chugai re-iterated that this interim report was published in November 1997 and was therefore not available at the time of preparation of the brochure. Furthermore, this abstract was an interim report of an incomplete study comparing lenograstim with filgrastim in the mobilization of autologous peripheral blood stem cells in patients with haematologic malignancies. The abstract stated that it was planned to randomise 80 patients to either 2 (for patients ≤80kg) or 3 (for patients >80kg) vials of lenograstim or a microgram equivalent dose of filgrastim. At the time of publication of this abstract only 28 patients had entered the study (15 randomised to lenograstim and 13 to filgrastim). Therefore it was not yet possible to draw any conclusions from these data.

The supplementary information relating to Clause 7.2 of the Code stated that: "Claims for superior potency in relation to weight are generally meaningless and best avoided unless they can be linked to some practical advantage, for example, reduction in side-effects or cost of effective dosage".

Chugai believed that this comparison was appropriate in this case. The paper by Mire-Sluis *et al* (1995) referred to earlier in the detail aid stated that a fundamental property of recombinant materials was that recombinant preparations of the same mass may not have the same biological activity, since their specific activities can vary. This property was reflected in the fact that one 263mcg vial of lenograstim contained 33.6 Million International Units whereas one 300mcg vial of filgrastim contained 30 Million Units. Therefore lenograstim contained 0.127MU/mcg and filgrastim contained 0.1MU/mcg. If dosing of rHuG-CSF was calculated from International Units (as mentioned in both the lenograstim SPC and the filgrastim SPC) then the 27% difference in activity per unit weight had important practical consequences for doctors, patients and health authorities.

## PANEL RULING

The Panel noted that Watts *et al* stated "In this study lenograstim was more potent than filgrastim on a weight for weight basis in terms of the rise in white cell count and the mobilization of GM-CFC.". The corresponding statement in the detail aid was "Lenograstim was shown to be more potent at mobilising progenitor cells than filgrastim on a weight for weight basis.". In the Panel's view the statement in the detail aid was more general than that in the clinical paper. The paper reported results generally in favour of lenograstim; the difference in the rise in white cell count was statistically significant (p=0.02), the difference in rise in GM-CFC levels was statistically significant (p=0.003) but the difference in rise in CD34+ cells was not statistically significant. The Panel considered that on balance the statement was not a fair reflection of the findings of the study. A breach of Clause 7.2 was ruled.

The Panel noted that the Kulkarni paper had not been published at the date of preparation of the detail aid and considered that its comments upon this paper at point 2 above applied here. The Panel ruled no breach of Clause 7.2 the Code.

**Complaint received** **12 February 1998**

**Case completed** **28 August 1998**

CASE AUTH/687/3/98

# SCHWARZ PHARMA v ASTRA

## MUSE formulary pack

**Schwarz Pharma made a number of allegations about a section entitled "Assessing the evidence base" in a formulary pack for MUSE (medicated urethral system for erection) produced by Astra. MUSE was a urethral stick for direct delivery of alprostadil to the male urethra. Schwarz marketed alprostadil in the form of an intracavernosal injection.**

**Schwarz alleged that the section was not an up-to-date evaluation of all the evidence as only one paper, Linet *et al* (1996), was used to present the case for intracavernosal alprostadil. The Panel noted that the data were selected according to the criteria for evidence based review and this was clearly stated. Astra had submitted that the Linet *et al* study was the only one on intracavernosal alprostadil that met the criteria. No breach of the Code was ruled.**

**Outcomes of an at-home phase of a transurethral alprostadil study were presented in a table. Schwarz said that it was unclear what dose level this data was based on. In a table relating to intracavernosal alprostadil the data were presented differently giving number needed to treat by dose level. Schwarz alleged a breach of the Code because the different formats and lack of clarity made it hard to make a meaningful comparison and a bias was produced in favour of transurethral alprostadil. The Panel considered that each table was clearly presented. There was no direct comparison of the numbers needed to treat for each medicine. The details appeared on different pages and the two tables of data were not directly opposite one another. The Panel did not accept that the presentation of data produced a bias in favour of transurethral alprostadil and ruled no breach of the Code.**

**Schwarz alleged that a table which presented reported adverse events, from two separate clinical trials of alprostadil delivered by the intracavernosal or the transurethral route, was misleading. The events for transurethral alprostadil and placebo, which were shown separately, should have been combined as the events were likely to be device and procedure orientated rather than related to the placebo medication. In addition the table referred to penile pain. Both the referenced studies not only gave figures for the number of patients who experienced penile pain but also for the number of applications which resulted in pain. Omitting data relating to the number of applications that resulted in pain misled by suggesting that there was a higher probability of experiencing pain with intracavernosal injection than with transurethral application. The Panel considered that the data given in the table was not complete enough to allow readers to understand the extent of the problem. To state only the number of men experiencing pain was not an accurate reflection of the data as a whole. A breach of the Code was ruled.**

**Astra accepted Schwarz's allegation that in the conclusion a statement that perhaps 85% of patients achieved a satisfactory response with intracavernosal alprostadil should have said 87%. A breach of the Code was ruled by the Panel in this regard.**

**Schwarz alleged that the statement "Whilst the transurethral route is associated with a somewhat lower success rate, its improved side effect profile and acceptability to patients make it the preferred therapeutic option for many patients" suggested that transurethral alprostadil was the preferred therapeutic option for many patients. Schwarz was not aware of any patient preference data to support this statement. The Panel noted that there was no data comparing patient acceptability of the two delivery systems. The Panel did not accept Astra's submission that the statement in question clearly related to the prescriber and not the patient. The Panel considered that the statement was misleading and ruled a breach of the Code.**

Schwarz Pharma Limited made a number of allegations about a formulary pack for MUSE (medicated urethral system for erection) produced by Astra Pharmaceuticals Ltd (MUSEFORM2397). MUSE was presented in the form of a urethral stick for direct delivery of alprostadil to the male urethra. Schwarz marketed alprostadil in the form of an intracavernosal injection. The complaint concerned Section 7 of the formulary pack entitled "Assessing the evidence base" which had been written by an independent expert in the field of evidence-based medicine and reflected his current opinion. The introduction to Section 7 clearly stated that it was written with the standards of evidence-based medicine in mind. Astra stated that it was these standards which formulary committees applied in considering applications for additions to fomularies.

Astra stated that the formulary pack was designed to provide balanced, fair and objective information on MUSE to enable formulary committee members to make an informed decision on the inclusion of MUSE on hospital formularies. It was distributed by Astra's specialist products sales force to doctors, pharmacists and urology nurses on formulary committees.

### 1 Failure to provide an up-to-date evaluation of all data

#### COMPLAINT

Schwarz alleged that the MUSE formulary pack contravened Clause 7.2 of the Code. In a developing field an up-to-date evaluation of all the evidence was difficult to achieve. However, Schwarz would contend that the choice of papers left something to be desired in that a paper by Linet *et al* was used exclusively to present the case for the use of intracavernosal alprostadil. Schwarz alleged that the exclusive use of this paper published in April 1996 did not present up-to-date data, nor could the exclusive use of this article be classified as an evaluation of all the evidence. Schwarz submitted that the presentation of the data was biased, selective and therefore misleading.

#### RESPONSE

Astra submitted that Section 7 was an evidence-based review. The introduction made clear the criteria which had been used to select the evidence, namely prospective

studies involving more than 100 patients. It clearly stated that there were more studies in the literature but that most did not conform to the accepted standards of evidence-based medicine as determined by the author, a recognised expert in such matters. Applying the stated criteria, four studies were therefore discussed, each dealing with a different treatment.

The study by Linet *et al* was the only study on intracavernosal alprostadil which met the criteria. Schwarz had offered no other references to challenge the conclusions based on this study.

Astra agreed that the data presented was selected according to the criteria used for evidence-based review. This was clearly stated in the introduction. Astra was therefore unclear how the presentation was biased or misleading and it therefore denied a breach of Clause 7.2 of the Code.

**PANEL RULING**

The Panel noted that the criteria for selection of the studies had been given in the introduction to the section. It further noted Astra's submission that the Linet *et al* study was the only one on intracavernosal alprostadil that met the criteria.

The Panel noted that Schwarz had not provided any material to support its allegation that up-to-date data had not been presented. The Panel therefore ruled no breach of Clause 7.2 of the Code.

**2 Table 3 and Table 4**

Outcomes of an at-home phase in the transurethral alprostadil study by Padma-Nathan *et al* (1997) were shown in Table 3. The outcomes reported were actual intercourse, orgasm, pain, trauma and dizziness. Calculations of numbers needed to treat or harm had been made. Table 4 dealt with patients achieving an erection judged sufficient for intercourse using intracavernosal injection of alprostadil. Numbers needed to treat had been calculated.

**COMPLAINT**

Schwarz stated that Table 3 presented what appeared to be an overall summary of data on transurethral alprostadil. It was unclear what dose level this data was based upon (was it highest dose, mean results, median results?) despite the fact that the data for individual dose level data was available in the Padma-Nathan *et al* paper. However, in the section on intracavernosal alprostadil the data was presented in a different format giving number needed to treat by dose level.

Given the different formats of data presentation and lack of clarity it was hard to make a meaningful comparison and therefore produced a bias in favour of transurethral alprostadil. A breach of Clause 7.2 was alleged.

**RESPONSE**

Astra submitted that the objective of the Padma-Nathan *et al* study was to evaluate the transurethral delivery system of alprostadil in the treatment of erectile dysfunction. The contents of Table 3 were clearly explained in the accompanying text. This made it clear that the data referred to the home phase of the study and that the dose was that which had worked in the clinic phase. No information was given in the paper about individual doses actually used and the response achieved with each, during the home phase, nor would it be relevant given the objective of the trial. It was thus incorrect that data was available on individual doses during this phase. The data was presented as it appeared in the paper, ie success or adverse event rate for total number of men treated. This data had been used to calculate the number need to treat or harm.

With regard to intracavernosal alprostadil, data from a study by Linet *et al* were presented in Table 4. The objectives of this study were to address the issues of effective dosing, efficacy and safety of the intracavernosal formulation of alprostadil. The data in Table 4 were again clearly explained in the accompanying text as detailing the dose response relationship with intracavernosal alprostadil. This paper presented the success rate for men treated at each of four doses, and the number needed to treat had been calculated from this. The second phase results of this study were described in the text as satisfactory after 87% of 13,762 injections. It was not possible to calculate number needed to treat from this data as the data referred to number of injections and not to number of patients.

With regard to the comparison of the data from these two studies, there was no direct comparison made of the numbers needed to treat between the two treatments, and given the different objectives of these studies Astra would not wish to do so. In the text, it stated in the relevant sections that the numbers needed to treat were one in three for transurethral alprostadil and "about two at higher doses" for intracavernosal alprostadil. Astra therefore found it surprising that Schwarz considered that the presentation of the data produced a bias in favour of transurethral alprostadil.

Astra was unclear how the presentation of data was misleading and denied a breach of Clause 7.2 of the Code.

**PANEL RULING**

The Panel noted that the at home phase of the Padma-Nathan *et al* study did not give details of the results with regard to the dose used.

The Panel considered that each table was clearly presented. There was no direct comparison of the numbers needed to treat for each treatment. The details appeared on different pages and the two tables of data were not directly opposite one another. The Panel did not accept that the presentation of the data produced a bias in favour of transurethral alprostadil. No breach of Clause 7.2 was ruled.

**3 Table 5: Adverse effects**

Table 5 gave details about adverse events observed in two separate clinical trials of alprostadil delivered by the intracavernosal or the transurethral route. Data was also included for transurethral placebo.

**COMPLAINT**

Schwarz alleged that Table 5 presented the reported adverse events in a misleading way. Schwarz submitted that the events for transurethral alprostadil and placebo should be combined as the placebo events were likely to be device and procedure orientated rather than related to the placebo medication. It was therefore misleading to separate them out.

There was also a significant omission of information in the table which Schwarz believed to be misleading. Both the referenced studies not only gave figures for the number of patients who experienced pain, but also for the number of applications which resulted in pain. The percentage of applications resulting in pain was the same for both products (11%). Omitting this fact misled the reader by suggestions that there was a higher probability of experiencing pain with intracavernosal injection than transurethral application of alprostadil. A breach of Clause 7.2 was alleged.

**RESPONSE**

Astra submitted that Schwarz's first comment about combining the active and placebo data did not seem to be valid. It was relevant to show the events separately as they were reported in two different groups. Clearly the events reported for transurethral alprostadil included those attributable to the active medication plus those attributable to the device, whereas the events reported for transurethral placebo were those attributable to the device.

Astra pointed out that penile pain was experienced by 50% and 33% of men and led to withdrawal from the study in 6% and 2.4% of men using intracavernosal and transurethral alprostadil respectively. Comparing the number of injections was a less informative measure, tending to bias the groups towards unity. This was because patients who experienced pain were likely to be withdrawn from study. It was therefore true that there was a higher probability of a patient experiencing pain with intracavernosal alprostadil.

Astra did not consider that this was misleading and denied a breach of Clause 7.2.

**PANEL RULING**

The Panel noted that penile pain was reported by 50% and 33% of men using intracavernosal alprostadil and transurethral alprostadil respectively. These were the only figures relating to penile pain given in Table 5. The published papers, however, showed that penile pain caused the withdrawal of 6% of men from intracavernosal therapy and 2.4% from transurethal therapy. As a percentage of the total number of applications penile pain occurred after 11% of intracavernosal injections and after 10.8% of transurethal administrations. Linet *et al* stated that, with regard to intracavernosal alprostadil, the difference between the number of men reporting penile pain (50%) and the number of injections resulting in penile pain (11%) indicated that many men had pain after only some injections. The authors also stated that although the pain was rated mostly as mild, it was a limiting factor for some men. The Panel considered that it was possible that for both forms of alprostadil, the difference in the number of men reporting pain and the number of injections or applications resulting in pain might be due, at least in part, to those men who experienced pain using the medicine less often than those who had not.

The Panel considered that the data given in Table 5 regarding penile pain was not complete enough to allow readers to understand the extent of the problem. The Panel considered that to only state the number of men experiencing pain was not an accurate reflection of the data as a whole. A breach of Clause 7.2 was ruled.

In consideration of this matter the Panel noted that the data regarding adverse events had been taken from two studies and presented in one table. The Panel queried whether such a presentation of the data invited readers to make direct comparisons between intracavernosal and transurethal alprostadil although the two products had not been directly compared. The Panel did not consider that the title of the table "Adverse effects observed in two separate clinical trials..." removed the impression that the data contained therein was directly comparable. The Panel also noted that with regard to transurethal alprostadil, data regarding the incidence of urinary tract infections had been excluded, as had the incidence of "other penile disorders" for intracavernosal alprostadil. The Panel requested that Astra be advised of its views.

**4 Conclusion: Factual error**

**COMPLAINT**

Schwarz drew attention to a factual error in the conclusion. The second paragraph stated that perhaps 85% of patients achieved a satisfactory response with intracavernosal alprostadil. However, in the cited reference and earlier in the material this figure had been given as 87%. A breach of Clause 7.2 was alleged.

**RESPONSE**

Astra agreed that this was a numerical error and would amend it accordingly. In fact, had Schwarz pointed this out to Astra directly, it would have changed it.

**PANEL RULING**

The Panel noted that the conclusion contained a factual error as alleged by Schwarz and accepted by Astra. The conclusion should have referred to 87% of patients achieving a satisfactory response instead of 85% as stated. The Panel considered that the conclusion was inaccurate and therefore ruled a breach of Clause 7.2 of the Code.

**5 Statement "Whilst the transurethral route is associated with a somewhat lower success rate, its improved side effect profile and acceptability to patients make it the preferred therapeutic option for many patients."**

**COMPLAINT**

Schwarz alleged that this statement, which was the final

sentence of the conclusion, suggested that transurethral alprostadil was the preferred therapeutic option for many patients. Schwarz was not aware of any patient preference data to support this statement. A breach of Clause 7.2 of the Code was alleged.

## RESPONSE

Astra submitted that this was not the intent of the author of the section. Each treatment might be the preferred therapeutic option for different groups of patients. When efficacy was the most important consideration, the intracavernosal injection might be the more appropriate. However, if overall risk/benefit profile was thought to be the key consideration, then the transurethral route might be the preferred option. The final two sentences read "Intracavernosal injection achieves high levels of efficacy but the potentially serious consequences of priapism and penile fibrosis limit the acceptability of this route. Whilst the transurethral route is associated with a somewhat lower success rate, its improved side effect profile and acceptability to patients make it the preferred therapeutic option for many patients".

The author therefore concluded that intracavernosal injection had high levels of efficacy but then considered the overall risk/benefit of the products. The discussion of the study by Padma-Nathan *et al* stated that "The delivery system was well accepted, as indicated by the favourable comfort ratings [transurethral application of alprostadil was rated as 'neutral', 'comfortable' or 'very comfortable' by at least 88% of men at each dose] and the 88 percent rate of study completion.". This study thus supported "acceptability to patients".

The statement made it clear that the transurethral route was the preferred therapeutic option for many, but not all, patients by virtue not just of patient acceptability but also of improved side effect profile. It was also clear that in this context the "preferred therapeutic option" related to the prescriber and not the patient.

The concluding statement was the opinion of the author and accordingly Astra did not consider it to be in breach of the Code.

## PANEL RULING

The Panel noted that there was no data comparing patient acceptability of the two delivery systems. There was no data to support the claim that the transurethral route was the preferred therapeutic option for many patients. The Panel did not accept that the statement in question clearly related to the prescriber and not the patient. The Panel considered that the statement was misleading and therefore ruled a breach of Clause 7.2 of the Code.

**Complaint received** **13 March 1998**

**Case completed** **25 June 1998**

CASE AUTH/693/4/98

# CONSULTANT CARDIOLOGIST v ROCHE

## Posicor mailing

**A consultant cardiologist alleged that a mailing for Posicor (mibefradil) issued by Roche was misleading. It had arrived shortly after the complainant had read a caution from the American College of Cardiology identifying an important interaction between mibefradil and simvastatin. The complainant understood a similar caution had been issued by the Department of Health. The mailing made great play of the low incidence of side effects of mibefradil and it was only under the fine print on the back page that the interaction with simvastatin was identified.**

**The Panel noted that it was Roche which had sent out details of the interaction in two "Dear Doctor" letters, rather than the Department of Health as stated by the complainant. The Panel appreciated the point that the complainant was making and the reasons why it was alleged that the mailing was misleading. The view of the Panel, however, was that the mailing was acceptable. Interactions had not been mentioned directly or indirectly in the promotional points made in the mailing and adequate reference had been made to them in the prescribing information. No breach of the Code was ruled.**

**Upon appeal by the complainant, the Appeal Board noted that the mailing had been sent out after the two "Dear Doctor" letters had been sent in November and February. The warning regarding the co-prescription of Posicor and simvastatin had been given in the prescribing information for the piece. The Appeal Board had some sympathy for Roche's view that there were difficulties in highlighting one interaction in a promotional item when other interactions might need to be considered by the prescriber. Nonetheless, in these unusual circumstances the Appeal Board considered that the mailing was not balanced as some mention of the interaction with simvastatin should have been made other than in the prescribing information. The Appeal Board ruled a breach of the Code.**

A consultant cardiologist complained about a mailing for Posicor (mibefradil) (ref: M673086/298) issued by Roche Products Limited.

### COMPLAINT

The complainant stated that the mailing arrived shortly after having read a caution distributed through the American College of Cardiology, identifying an important interaction between mibefradil and simvastatin. The complainant believed that a similar caution had been issued through the Department of Health in the UK. The mibefradil mailing made great play of the low incidence of side-effects: "Incidence of side effects comparable to placebo at usual 50 mg o.d. dose" appeared in the centre of the item. It was only in the fine print on the back page under drug interactions that the interaction with simvastatin was identified. Even then it was mentioned last in the drug interactions and was preceded by the statement "May be safely administered with commonly used drugs such as diuretics ..., most lipid lowering agents (see below), ..." The final sentence of drug interactions was "Concomitant administration with simvastatin should be avoided".

Mibefradil was being promoted for use in both hypertension and angina. Simvastatin was probably the leading drug in its class in the market in the UK and widely promulgated guidelines advised the use of simvastatin and other medicines in patients who had angina. It was for this reason that the complainant believed that the promotional material on mibefradil was misleading.

### RESPONSE

Roche stated that the promotional piece was a hospital mailer which was mailed in early March 1998 to hospital consultants in cardiology, cardiothoracic surgery, renal, general physicians, diabetology, clinical pharmacology and respiratory medicine. The mailer was actually printed in February 1998. The date of preparation was December 1997.

In response to the comments made by the complainant, Roche made the following points:

1 The prescribing information was in Roche's view clear and unambiguous. The content of the summary of product characteristics (SPC) and the prescribing information had been agreed with the Medicines Control Agency (MCA) and both the prescribing information and the SPC clearly stated that the co-prescription of mibefradil and simvastatin should be avoided. Roche's salesforce were all trained to disseminate this information.

2 Mibefradil was indeed well tolerated, on the basis of clinical trial information. This should not be confused with a drug interaction, particularly where the interaction mentioned (mibefradil and simvastatin) led to an adverse reaction attributed to simvastatin and not to mibefradil.

3 All fully registered doctors in the UK (approximately 110,000) were notified of the interaction between simvastatin and mibefradil in a letter from Roche's medical adviser dated 25 November 1997, several months prior to this mailing. This "Dear Doctor" letter was issued at the company's own initiative, not the Department of Health or MCA as the complainant suggested. As an ethical company, Roche considered that it should impose an urgent safety restriction on the co-prescription of mibefradil and simvastatin. A copy of the letter was supplied for information.

4 The "Dear Doctor" letter of November 1997 was followed up by an informational letter in February 1998, again from Roche's medical adviser, to all hospital doctors from consultant down to registrar grade in the following specialities: cardiology, geriatrics, renal, diabetology, general medicine and clinical pharmacology, together with hospital pharmacists. This second letter provided practical prescribing advice on the co-prescription of statins with mibefradil, to clarify the situation further. A copy of this "Dear Doctor" letter was also supplied. It was important to note that mibefradil might be safely co-prescribed with other statins, such as

pravastatin or fluvastatin.

5 The promotional piece was not designed to promote co-prescription of mibefradil with simvastatin to patients with angina. In Roche's opinion, it simply explained the mode of action of the medicine and introduced it as an alternative agent in essential hypertension and/or stable angina. The intention of a mailer was to generate interest and prompt queries for further information. Nowhere in the main body of the piece was there the implication that mibefradil did not have drug interactions and the prescribing information made clear reference to simvastatin, as mentioned above.

Roche had provided accurate, balanced information about mibefradil, especially considering the previous "Dear Doctor" letters. The company did not believe that there had been any breach of the Code.

## PANEL RULING

The Panel noted that the item was of complex physical form and that when it was partially unfolded the centre page said "Incidence of side effects comparable to placebo at usual 50mg o.d. dose". This statement was consistent with the prescribing information and the SPC. The prescribing information stated "In clinical trials discontinuation of Posicor due to side effects was similar to placebo" and "Incidence of side effects of Posicor 50mg was similar to placebo, ..." There was a difference between a side effect and an interaction.

In relation to the interaction between mibefradil and simvastatin, the Panel noted that the prescribing information stated that Posicor could be safely administered with "... most lipid lowering agents (see below), ...". This was followed a little further on by the statement "Concomitant administration with simvastatin should be avoided". The SPC stated that combined use of Posicor with HMG CoA reductase inhibitors simvastatin and lovastatin should be avoided.

The Panel appreciated the point that the complainant was making in the allegation and the reasons why it was alleged that the promotional item was misleading. The view of the Panel was, however, that the mailing was acceptable. Interactions had not been mentioned directly or indirectly in the promotional points made in the mailing and the Panel considered that adequate reference to them had been made in the prescribing information. No breach of Clause 7.2 of the Code was ruled.

## APPEAL BY THE COMPLAINANT

The complainant submitted that Roche was of course completely accurate in a legal sense that the potential interaction between Posicor and simvastatin was identified in the fine print of the prescribing information. The company was also correct in indicating that it had highlighted the interaction between the two medicines in a "Dear Doctor" letter dated 25 November 1997 followed up by a further "Dear Doctor" letter in February 1998. This might mean that the company had fulfilled its legal obligations to let the profession know of this potential fatal interaction leaving the onus of responsibility for making sure that Posicor was not co-prescribed with the most commonly prescribed lipid lowering agent to the prescribing physician and pharmacist. Roche was also correct legally in drawing the distinction between a side-effect of a drug prescribed on its own, and a drug interaction. The complainant was not sure that this fine distinction would cut much ice with a patient who had been co-prescribed Posicor and simvastatin, and had suffered the devastating effects of developing rhabdomyelitis.

The complainant was disappointed by the response from Roche and the ruling of the Panel. Doctors were bombarded with a fantastic amount of information and if Roche considered the interaction of Posicor and simvastatin important enough to send out two "Dear Doctor" letters then surely it could have considered this information important enough to feature prominently in its promotional material for the medicine. The complainant considered that it was disingenuous of the company to state "The intention of a mailer was to generate interest and prompt queries for further information". The mailer identified the significant advantages of the medicine in angina and hypertension and was surely intended to encourage prescription.

The complainant considered that it would be sensible for the ABPI to apply the same standards to the advertising of its products as the Advertising Standards Authority applied to the advertising of products to the general public. These were that an advertisement should be legal, decent, honest and fair. The complainant submitted that it would be "decent" of the company to remind doctors in a prominent way of an important side-effect that it had highlighted in a previous mailing some weeks earlier, and that it was "fair" to patients who might suffer catastrophic harm for this information to be more prominently displayed in promotional material for Posicor.

## RESPONSE FROM ROCHE

Roche noted that the complainant in essence agreed that it had not breached the Code from a technical viewpoint and therefore, the company saw no need to reiterate the points made in its earlier response. However, Roche asked the Appeal Board to consider those points.

Roche noted that the complainant seemed to take issue with the requirements of the Code itself, rather than with the technicalities of this particular complaint. Thus, the complainant suggested it would be "decent" of the company to remind doctors in a prominent way of an important interaction highlighted in an earlier "Dear Doctor" letter. However, the main purpose of the "Dear Doctor" letter was to highlight a new potential drug interaction not previously contained in the SPC. Therefore, although the company had some sympathy for the complainant's opinion, it would be inappropriate to highlight one particular interaction on a promotional item, when other possibly equally important interactions and undesirable effects should be considered by the prescriber. The best place to summarise these considerations was in the prescribing information, which was prominently displayed in this item.

## FURTHER COMMENTS FROM THE COMPLAINANT

There were no further comments from the complainant.

### APPEAL BOARD RULING

The Appeal Board noted that Posicor had been withdrawn in early June. The company had explained that the withdrawal had been due to interactions with a number of products not just simvastatin.

The Appeal Board noted that the mailing had been sent out after the two "Dear Doctor" letters had been sent in November and February. The warning regarding the co-prescription of Posicor and simvastatin had been given in the prescribing information for the piece. The Appeal Board had some sympathy for the view that there were difficulties in highlighting one interaction in a promotional item when other interactions might need to be considered by the prescriber. Nonetheless, in these unusual circumstances the Appeal Board considered that the mailing was not balanced as some mention of the interaction with simvastatin should have been made other than in the prescribing information. The Appeal Board ruled a breach of Clause 7.2 of the Code.

The complainant's appeal was successful.

**Complaint received** 8 April 1998

**Case completed** 14 August 1998

---

**CASE AUTH/694/4/98**

# GLAXO WELLCOME v ASTRA

## Oxis Turbohaler 12 leavepieces

**Glaxo Wellcome complained about three leavepieces for Oxis Turbohaler 12 (eformoterol) which had been issued by Astra.**

**The leavepieces made the claim "The only long-acting bronchodilator to have demonstrated 12 month outcome benefits" but Glaxo Wellcome alleged that this breached the Code because twelve month data had been reported for salmeterol (Glaxo Wellcome's Serevent) in two major publications. The Panel noted Astra's assertion that two claims which followed the claim in question defined the outcome benefits but considered that the presentation and layout made this connection far from clear. In the Panel's view, most readers would see each claim in isolation and without an explanation would take the claim in question to mean that the Oxis Turbohaler 12 was the only bronchodilator for which there was data covering twelve months' use. A breach of the Code was ruled.**

**The claim "A significant advance in asthma management" was alleged by Glaxo Wellcome to be a hanging comparison as it was suggesting that Oxis Turbohaler was an advance but not clarifying what it was an advance from. The Panel did not consider that the heading "A significant advance in asthma management" could be regarded as a "hanging comparison" as meant by that term in the supplementary information to the Code. It differed in substance and meaning from the "A is better" type of claim in which there was an apparent, but undeclared, comparator that A was claimed to be better than. No breach of the Code was ruled in that regard.**

Glaxo Wellcome UK Limited complained about three leavepieces relating to Oxis Turbohaler 12, eformoterol, (refs: OXIS 97 2449, OXIS 97 2634 and OXIS 97 2644C) which had been issued by Astra Pharmaceuticals Ltd. Astra said that leavepiece 2449 was a hospital dosage card which was left with hospital physicians following calls by Astra representatives. Leavepiece 2634 was a GP dosage card which was left with general practitioners and practice nurses following calls by Astra representatives. Leavepiece 2644C had been used in a one-off launch mailing to general practitioners and practice nurses.

### 1 "The only long-acting bronchodilator to have demonstrated 12 month outcome benefits."

This claim appeared in all three versions of the leavepiece as one of four bullet points.

#### COMPLAINT

Glaxo Wellcome stated that this claim seemed fairly self-explanatory. Glaxo Wellcome had drawn Astra's attention to the fact that in two major publications, the European Respiratory Journal (Britton *et al* (1992)) and Thorax (Lundback *et al* (1993)), quite clearly twelve month data for salmeterol was reported. Glaxo Wellcome strongly asserted that the leavepieces were in breach of Clause 7.2 of the Code.

#### RESPONSE

Astra stated that it did not agree that the use of this claim was in breach of Clause 7.2 of the Code. The statement related to the FACET study data reported by Pauwels *et al* in the New England Journal of Medicine 1997. The outcome benefits referred to were clearly presented in the three leavepieces: significantly reduces severe and mild asthma attacks in addition to high or low dose steroid; significantly reduces the need for rescue medication compared to steroid alone. The FACET data provided the first data on outcome benefits over a 12 month period in asthmatic patients controlled on inhaled steroids. The importance and exclusivity of these outcome benefits, for eformoterol, lay not only in the results obtained over 12 months but also in the design of the trial itself.

All patients in the four arms of the study were controlled throughout on fixed doses of one inhaled steroid, thus meaning any resultant outcomes, with the addition of eformoterol, could clearly be assessed. This was further enhanced by the trial including placebo arms throughout the 12 month period, so that the true benefits of the long-acting ß-agonist could be measured. As a result of the design of the study and the consequent measurements over 12 months, the results of the trial were the first to clearly demonstrate the benefits of adding in a long-acting

ß-agonist to regular inhaled steroids. FACET studied clinical outcomes – number of attacks over 12 months, use of rescue medication. This differed from measurement of lung function.

The strength of the FACET study lay in the outcome benefits demonstrated. These were defined in what were clinically relevant terms and what were accepted to be true clinical outcomes, both from a physician's and a patient's perspective, ie reduction of asthma attack rates (both mild and severe).

The measurement of lung function in isolation would not necessarily define when there was a significant asthma attack or exacerbation. The study supported the conclusion that clinical judgement was an adequate means by which to define severe exacerbations. This was supported by the fact that the majority of the severe exacerbations were defined clinically as needing courses of oral steroids and not based on lung function measurements in isolation.

The strength of the FACET data and the patient populations studied, whilst all controlled on fixed doses of inhaled steroids, meant the true outcome benefits of eformoterol over 12 months could be seen.

Astra did not question that 12 month data existed for salmeterol. However the data, Astra believed, did not constitute true outcome benefits. The trials that Glaxo Wellcome referred to in its complaint consisted of a 3 month period of close observation followed by a 9 month extension period in both cases. The 9 month "extension" was simply to collect safety data as well as intermittent lung function data at clinic visits. In both study papers there was data clearly presented for the initial 3 month period, although limited data was available for the 9 month extension periods. In addition, the dosage of inhaled steroids/additional therapies patients received were not clearly defined or controlled in either study. As a result, a heterogeneous treatment population was studied. Indeed, not all patients received inhaled steroids in the studies (40% of asthmatic patients in the Lundback study did not receive inhaled steroids throughout the 12 months). Additionally, the lack of placebo control meant limited interpretation of any results, as it was not possible to state what the true benefits of salmeterol were.

For all the above reasons, Astra believed that the salmeterol data Glaxo Wellcome referred to did not constitute true 12 month outcome benefits for asthmatic patients treated with inhaled steroids and long-acting ß-agonists.

Based on the nature of the data collected over 12 months and the benefits demonstrated in the FACET study, Astra believed it was accurate to make a claim that eformoterol was the only long-acting bronchodilator to demonstrate true outcome benefits over a 12 month period, ie a significant reduction in severe and mild asthma attacks in addition to high or low dose steroid and a significant reduction in rescue medication, compared to steroid alone.

Astra therefore denied a breach of Clause 7.2.

## PANEL RULING

The Panel examined the studies referred to by the parties.

The Panel noted that the Britton *et al* study, referred to by Glaxo Wellcome, had involved a three month comparison of the efficacy and tolerability of salmeterol 50mcg twice a day with salbutamol 200mcg four times a day. For the following nine months, safety and clinic lung function had been monitored on salmeterol 50mcg twice a day compared with salbutamol 200mcg twice a day. It was concluded that both treatments were well tolerated throughout the twelve months of treatment. The Lundback *et al* paper, also referred to by Glaxo Wellcome, had compared salmeterol 50mcg twice a day with salbutamol 400mcg four times a day. During the first three months detailed assessment of efficacy was made. Patients continued for a further nine months with the dose of salbutamol reduced to 400mcg twice daily. During this period lung function was measured at the clinic and safety data were collected. Neither product was associated with any worsening of control of asthma.

The FACET study reported by Pauwels *et al* and referred to by Astra involved comparisons of four treatments twice daily; these being 100mcg of budesonide plus placebo, 100mcg of budesonide plus 12mcg of eformoterol, 400mcg budesonide plus placebo and 400mcg of budesonide plus 12mcg of eformoterol. Treatment continued for one year. Frequency of exacerbations of asthma symptoms and lung function were compared. It was concluded that the addition of eformoterol to budesonide therapy improved symptoms and lung function without lessening the control of asthma.

The Panel accepted that there were differences between the Britton and the Lundback studies on the one hand and the FACET study (Pauwels *et al*) on the other; the latter having continued in one mode for the full year.

The Panel examined the leavepieces and noted that each listed four claims, in bullet point style, all of which were given equal significance. The claim in question, "The only long-acting bronchodilator to have demonstrated 12 month outcome benefits", was always followed by the two claims "Significantly reduces severe and mild asthma attacks in addition to high or low dose steroid" and "Significantly reduces the need for rescue medication compared to steroid alone". The Panel noted Astra's submission that the latter two claims defined the outcome benefits referred to in the claim in question but considered that the presentation and layout made this connection far from clear. In the Panel's view the majority of readers would see each claim in isolation and, without an explanation of the term "outcome benefit" would take the claim in question to mean that the Oxis Turbohaler 12 was the only long-acting bronchodilator for which there was data covering 12 months' use. This claim was insufficiently qualified and was therefore misleading. The Panel ruled a breach of Clause 7.2 of the Code.

### 2 "A significant advance in asthma management"

This claim appeared in bold as the main heading on the hospital dosage card (OXIS 97 2449). Bullet points, in a lesser size type, below the heading made clinical claims for the Oxis Turbohaler 12.

### COMPLAINT

Glaxo Wellcome said that it believed that this heading constituted a hanging comparison in that it was suggesting that Oxis Turbohaler was an advance but not clarifying as to what it was an advance from. Glaxo Wellcome alleged a breach of Clause 7.2 of the Code.

### RESPONSE

Astra said that it did not agree that the use of this heading was in breach of Clause 7.2 of the Code.

It was clear from the layout of the piece that the heading referred to the accompanying bullet points, referenced to the FACET trial. The FACET trial was designed specifically to answer concerns and management issues on the use of long-acting ß-agonists, which had not been fully answered by previous studies in this area. The trial set out to answer the key questions:

- Did asthma control continue in the long-term when a long-acting ß-agonist was used regularly?
- When an asthmatic patient was uncontrolled on low-dose steroid, should the steroid dose be increased or a long-acting ß-agonist added?
- Was there further room for improved asthmatic control when a long-acting ß-agonist was added to high dose inhaled steroids?

All were important issues in the management of asthma which had not been fully answered to date.

The four bullet points under the heading related to the important findings from the FACET study and did constitute a significant advance for the management of asthmatic patients on inhaled steroids.

The heading "A significant advance in asthma management" was not a hanging comparative and was qualified by the underlying bullet points.

Astra therefore denied a breach of Clause 7.2.

### PANEL RULING

The Panel did not consider that the heading "A significant advance in asthma management" could be regarded as a "hanging comparison" as meant by that term in the supplementary information to Clause 7.2 of the Code. It differed in substance and meaning from the "A is better" type of claim in which there was an apparent, but undeclared, comparator that A was claimed to be better than. No breach of the Code was ruled in this regard.

**Complaint received** **14 April 1998**

**Case completed** **18 June 1998**

---

**CASES AUTH/695/4/98 and AUTH/696/4/98**

# CONSULTANT PHYSICIAN v JANSSEN-CILAG and ORGANON

## Risperdal mailing offer

**A consultant physician complained about a mailing for Risperdal issued by Janssen-Cilag and Organon Laboratories. A reply paid card attached to the mailing stated "I would like a representative to deliver my complimentary mini dictaphone" followed by a box to tick. Space was provided for the doctor to fill in his name and address and stamp the card with the surgery stamp. The complainant alleged that the card was a simple bribe to doctors to agree to a representative visiting.**

**The Panel noted that when representatives received their supply of mini dictaphones they were also to be advised of the requirements of Clause 15.3 via a company memorandum. The memorandum stated that if an interview with a clinician was refused then representatives had nonetheless to leave the mini dictaphone. The Panel considered, however, that the impression given to recipients of the card was that it was necessary to see a representative in order to receive a mini dictaphone. No other delivery option was given. Each company was ruled in breach of the Code.**

**Upon appeal by both companies, the Appeal Board considered that the wording on the card clearly stated how the mini dictaphone would reach recipients. Doctors would know that a representative would be calling and could not be left with the impression that it would be delivered in any other way. Readers would assume that in order to receive a mini dictaphone they were obliged to see the representative and this was unacceptable. The Appeal Board upheld the Panel's ruling that the Code had been breached.**

**In the Appeal Board's view, if reply paid cards referred to representatives delivering items then recipients should be given an alternative delivery option or an explanation that there was no obligation to grant the representative an interview.**

A consultant physician in the care of the elderly complained about a mailing for Risperdal issued by Janssen-Cilag Ltd and Organon Laboratories Limited. A reply paid card attached to the mailing stated "I would like a representative to deliver my complimentary mini dictaphone" which was followed by a box to tick. Space was provided for the doctor to fill in his name and address and to stamp the card with the surgery stamp. The card was to be signed and dated. The mailing had been sent to geriatricians and psychogeriatricians.

### COMPLAINT

The complainant said that he had been concerned for some time about relationships between pharmaceutical companies and doctors. He strongly believed that there were faults on both sides but the card, which came through the post, was a simple bribe to doctors to agree to a representative visiting. He considered that it was not an acceptable advertisement and suggested that it breached the Code.

## RESPONSE

Responding on behalf of both companies, Janssen-Cilag said that the mailer in question was part of a recent campaign in elderly psychosis which involved the offer of a complimentary mini dictaphone to interested physicians.

The reply paid card relating to this offer required the physician to indicate whether he or she would like the item delivered by the local company representative. It in no way inferred that the delivery of the item obliged them to receive a promotional call from that representative. Janssen-Cilag pointed out that the representative team involved with this campaign had all recently received training on the Code and were fully aware of the requirements of Clause 15.3.

Janssen-Cilag noted the recent ruling (Case AUTH/646/11/97) regarding reply paid cards but pointed out that the reply paid card found in breach of the Code included a section requiring a convenient time to be stated, thus inferring a possible link between delivery of the item and an obligation to see the representative. This reply paid card did not. Janssen-Cilag also pointed out that it was not unusual within the industry for representatives to deliver requested items whether this was stated on the reply paid card or not.

Janssen-Cilag provided a mini dictaphone and an invoice to show that the cost per item was £4.99, excluding VAT.

Janssen-Cilag confirmed that a small number of mini dictaphones would be dispatched to each representative for delivery with a memorandum reminding them as to the requirements of Clause 15.3 of the Code. A copy was supplied.

## PANEL RULING

The Panel noted the outcome of Case AUTH/646/11/97 in which the Appeal Board had ruled a breach of Clause 15.3 of the Code in relation to a reply paid card offering a calendar which stated "I understand that a representative will deliver this item". Space on the card was provided for the doctor to indicate the time and day most convenient for delivery. The Appeal Board had considered that the wording and layout of the card was such that readers would assume that in order to receive the calendar they were obliged to see a representative.

Despite the fact that there was no space for the doctor to indicate a time and day to call, the Panel could see no difference in substance between the arrangements in Case AUTH/646/11/97 and the arrangements in the present case where the card said "I would like a representative to deliver my complimentary mini dictaphone". The Panel noted that when the representatives received their supply of mini dictaphones they were also to be advised about the requirements of Clause 15.3 via a company memorandum. The memorandum stated that if an interview with a clinician was refused then representatives had to ensure that they nevertheless left the mini dictaphone for the clinician. The Panel considered, however, that the impression given to recipients of the reply paid card was that it was necessary to see a representative in order to receive the mini dictaphone. No other delivery option was given.

A breach of Clause 15.3 of the Code was ruled in relation to each company.

The Panel considered that the item itself was not unacceptable. It was relevant to the practice of medicine and cost no more than £5, excluding VAT, as specified in the Code.

## APPEAL BY JANSSEN-CILAG AND ORGANON

On behalf of both companies, Janssen-Cilag stated that it had some difficulty in understanding the ruling of a breach of Clause 15.3 of the Code. Clause 15.3 stated that "Representatives must not employ any inducement or subterfuge to gain an interview". It was not clear from the complaint that any of the representatives had indeed employed any inducement or subterfuge. It would appear that the complainant was concerned that Janssen-Cilag was employing an inducement or subterfuge which was not strictly prohibited by Clause 15.3. It would also appear that the complainant had major concerns about the relationship between doctors and the industry. Janssen-Cilag submitted that maybe the complainant presented a view that was not representative of his colleagues.

Janssen-Cilag stated that it was common industry practice to attach reply paid cards offering an item that was intended to be of use to potential recipients. The reason for so doing was simple. Representatives' interviews with doctors were becoming increasingly difficult to obtain and the industry offered these items in the hope that by giving the representative proper cause to be in the surgery or department (if a hospital) that a spontaneous interview might ensue, if the doctor was available and willing. If such a spontaneous interview was refused, and this might well happen since the doctor was under no obligation to allow the interview, the representative was instructed to leave the item for the doctor.

Janssen-Cilag stated that, hence, at no point did the representative, or the company, employ any inducement or subterfuge to gain an interview. What they had done was use the item as a mechanism to allow the requesting of a spontaneous interview which Janssen-Cilag understood was not in breach of the Code.

Janssen-Cilag appreciated that in Case AUTH/646/11/97 the Appeal Board had ruled that the wording and layout of the card led the reader to assume an obligation to allow an interview with the representative. The company also appreciated that its case might superficially appear similar to that case. Since each case was judged on its own merits, Janssen-Cilag would like to think that the ruling in Case AUTH/646/11/97 did not necessarily have to be borne in mind when its case was considered afresh.

Janssen-Cilag stated, however, that even if its case was compared to Case AUTH/646/11/97 there were important differences in the wording of the reply paid card. In its case Janssen-Cilag did not request a convenient time and date for delivery. The company only implied that a representative would deliver the item. The Collins English Dictionary's definition of 'deliver' was 'to carry goods to a destination' which was simply what the representative would do (action one). The representative would then take the opportunity to request an interview with the physician (action two) who would be at liberty to refuse. If an interview was refused the item would be left

anyway. Action two was completely separate to action one and was an action undertaken by all company sales representatives every working day. Action one was the only action mentioned on the reply paid card and was the only action that a physician would agree to by returning that card.

### APPEAL BOARD RULING

The Appeal Board considered that the wording on the reply paid card, "I would like a representative to deliver my complimentary mini dictaphone" clearly stated how the mini dictaphone was going to reach the recipients. Doctors would know that a representative would be calling and could not be left with the impression that the mini dictaphone would be delivered any other way.

The Appeal Board noted that a memorandum had been sent to the representatives reminding them of their obligations under Clause 15.3 of the Code. The memorandum was dated 29 April 1998 which was after the companies had been notified of the complaint.

Representatives were told in the memorandum that they would shortly be receiving some reply paid cards requesting a mini dictaphone and that they should neither state nor infer that the delivery of the mini dictaphone obliged the doctor to grant them an interview. The Appeal Board considered, however, that the reply paid card gave a different impression and that readers would assume that in order to receive the mini dictaphone they were obliged to see the representative. This was unacceptable. No other option had been given. The Appeal Board upheld the Panel's ruling of a breach of Clause 15.3 in relation to each company.

The appeals therefore failed.

In the Appeal Board's view, if reply paid cards referred to representatives delivering items then recipients should be given an alternative delivery option or an explanation that there was no obligation to grant the representative an interview.

**Complaint received** 20 April 1998

**Case completed** 3 July 1998

---

**CASE AUTH/699/4/98**

# ORGANON v SERONO

## Gonal-F detail aid

**Organon Laboratories complained about a detail aid for Gonal-F (follitropin alpha) which had been issued by Serono Laboratories.**

**Organon stated that the phrase "... comes the standard for a new era" was reinforced by the image of a gold ingot and hallmarks with the obvious intention of suggesting a gold standard status. Organon alleged that this was an exaggerated claim. The Panel did not accept that the phrase was an exaggerated claim. Gonal-F was the first recombinant follicle stimulating hormone (FSH) product and as such it would be setting the standard. There was no mention of other recombinant FSH products and Gonal-F was discussed only in the context of urinary derived products. No breach of the Code was ruled.**

**A page headed "Gonal-F raising the standard" compared the clinical pregnancy rate per initiated cycle of recombinant human follicle stimulating hormone (r-hFSH) with urinary/high purity urinary (u-hFSH/u-hFSH HP) products. The results of three studies were shown separately on a bar chart. Organon alleged that none of the studies referred to showed a significant difference between recombinant FSH and urinary FSH but this was implied by the artwork and the heading. The Panel considered that the combination of the headline, the visual difference in favour of recombinant FSH shown in the bar chart and the footnote "An additional older study presented in 1993 showed no significant difference in pregnancy rate between the two products" gave the impression that the three studies showed statistically significant differences but that was not so. The page was misleading and was ruled in breach. A further breach was ruled because the bar chart gave the visual impression that there was a difference between the products which was not borne out by the statistics.**

**Two pages respectively headed "Gonal-F your hallmark for success" and "Gonal-F creating new standards" showed six bar charts depicting differences between Gonal-F and u-hFSH HP for various parameters. All the bar charts except one showed a statistically significant advantage for Gonal-F. The bar chart headed "Clinical Pregnancy Rate" showed a visual difference in favour of Gonal-F but this was not statistically significant. Organon alleged that the claim with the bar chart "22% more pregnancies/start cycle" constituted an exaggerated and unsubstantiated claim and that the use of the study to demonstrate improved efficacy for a number of other parameters constituted unbalanced claims in view of the other available data on Gonal-F. The Panel considered that readers would gain the impression that the 22% difference between Gonal-F and u-hFSH HP was statistically significant but this was not so. The claim was misleading and was ruled in breach. No breach was ruled in relation to the use of the study. It was the only comparative study of Gonal-F versus a currently available urinary FSH product. The only other available data were old studies using comparators not currently marketed.**

**A page headed "Gonal-F improving the standard of effectiveness" showed a chart comparing the benefits of Gonal-F and u-hFSH HP. The chart in effect stated that "Higher pregnancy rate per cycle" gave the opportunity for increased efficiency through improved effectiveness and increased value. Organon alleged that the Code had been breached by stating that a higher pregnancy rate was found. Improved effectiveness could not be claimed. The Panel noted that the claim "Higher pregnancy rate per cycle" was referenced to a study which had shown no statistically significant difference between Gonal-F and u-hFSH HP. It was misleading and was ruled in breach.**

Organon Laboratories Ltd made a number of allegations about a detail aid (ref F8671097) for Gonal-F (follitropin

alpha) issued by Serono Laboratories (UK) Limited. Serono although not a member of the ABPI had nevertheless agreed to comply with the Code.

Serono stated that the detail aid had been distributed at the British Fertility Society Meeting in December 1997 and by sales representatives during December 1997 to early March 1998. Following an informal approach by Organon, it had already discontinued use of the item.

### 1 Front cover (page 1) - "... comes the standard for a new era"

#### COMPLAINT

Organon said that this phrase was reinforced by the image of a gold ingot and hallmarks, with the obvious intention of suggesting a gold standard status. Organon alleged that it was an exaggerated claim and use of an absolute in breach of Clause 7.8 of the Code.

#### RESPONSE

Serono refuted the allegation that this was an exaggerated claim and use of an absolute, in breach of Clause 7.8.

Serono stated that it might be useful to explain that the "new era" in the supply of gonadotrophins referred to was the introduction of recombinant follicle stimulating hormone (FSH) products such as Gonal-F and Puregon (Organon) which were of very high purity and were not derived from human urine, as was the case for traditional fertility products.

Serono's phrase "... the standard for a new era" referred to Gonal-F setting the standard for recombinant FSH preparations, being the first such product licensed and made available in Europe.

Serono noted that Clause 7.8 and the accompanying supplementary information did not mention prohibition of "absolutes". However, if Organon was implying that Serono's claim was a "superlative" it had to disagree. Serono's position was that Gonal-F was a high quality product which should be considered as a "benchmark". Nowhere in the piece had Serono claimed that Gonal-F was the best treatment, or that other recombinant products did not meet this standard. Indeed the piece focused on the difference between recombinant FSH and urinary FSH.

#### PANEL RULING

The Panel did not accept the allegation that the phrase "... comes the standard for a new era" was an exaggerated claim. The Panel noted that Gonal-F was the first recombinant FSH product and as such it would be setting the standard. There was no mention on the front cover or in the rest of the detail aid of other recombinant FSH products, Gonal-F was discussed only in the context of the urinary derived products. The Panel therefore ruled no breach of Clause 7.8 of the Code.

### 2 Page 3 headed "Gonal-F raising the standard"

The page compared the clinical pregnancy rate per initiated cycle of recombinant human follicle stimulating hormone (r-hFSH) with the urinary/high purity urinary (u-hFSH/u-hFSH HP) products. The results of three studies were shown separately on a bar chart.

#### COMPLAINT

Organon said that none of the studies referred to showed a significant difference between recombinant FSH and urinary FSH. However, this was implied by the artwork and the heading "Gonal-F raising the standard". Furthermore, the footnote at the bottom of the bar chart "An additional older study presented in 1993 showed no significant difference in pregnancy rate between the two products", would leave the perception that the three studies referred to in the bar chart above did show a significant difference. Organon noted that the summary of product characteristics (SPC) for Gonal-F stated in Section 4.2 that "The equivalency of the potency of Gonal-F and urinary FSH-containing preparations has not been definitively proven". This statement was in contrast to the SPC for the rival product Puregon which stated that it was more potent. Organon alleged that this page breached Clause 7.2 of the Code with its misleading information since no significant difference had been demonstrated and Clause 7.6 with the misleading bar chart implying a major improvement in the product.

#### RESPONSE

Serono said that it did not accept that the heading "Gonal-F raising the standard" and the associated bar chart were in breach of Clauses 7.2 or 7.6.

On all pages of the detail aid, all differences which reached statistical significance were clearly marked with an asterisk and associated p value.

Serono agreed that the differences in pregnancy rate per initiated cycle between the two products compared were not statistically significant, and it did not claim any statistically significant difference. Since the artwork showed data derived directly from the clinical paper, Serono did not accept that this depiction was misleading.

#### PANEL RULING

The Panel considered that the combination of the headline "Gonal-F raising the standard", the visual difference in favour of recombinant FSH shown in the bar chart and the footnote below "An additional older study presented in 1993 showed no significant differences in pregnancy rate between the two products" gave the impression that the three studies showed statistically significant differences with regard to clinical pregnancy rates per initiated cycle. This was not so. None of the three studies had showed statistically significant differences between r-hFSH and u-hFSH / u-hFSH HP. The Panel therefore ruled that the page was misleading in breach of Clause 7.2 of the Code. The Panel also considered that the bar chart was misleading as it gave the visual impression that there was a difference between the products which was not borne out by the statistics. A breach of Clause 7.6 of the Code was ruled.

### 3 Page 4 headed "Gonal-F your hallmark for success" and page 5 headed "Gonal-F creating new standards"

These two pages showed six bar charts depicting differences between Gonal-F and u-hFSH HP for various parameters from a study by Bergh *et al* 1997. All the bar charts except one showed a statistically significant advantage for Gonal-F. The bar chart headed "Clinical Pregnancy Rate" showed a visual difference in favour of Gonal-F but this was not statistically significant.

#### COMPLAINT

Organon referred to the bar chart headed "Clinical Pregnancy Rate" which was followed by a claim for "22% more pregnancies/start cycle". Since no statistical significance was given for this parameter, Organon alleged this constituted an exaggerated and unsubstantiated claim in breach of Clauses 7.8 and 7.2 of the Code.

Organon alleged that use of the Bergh study to demonstrate improved efficacy for a number of other parameters on pages 4 and 5 of the detail aid constituted unbalanced claims in view of the other available data on Gonal-F and the statement in the SPC in breach of Clause 7.2 of the Code.

#### RESPONSE

Serono said that in the case of the Bergh results quoted on pages 4 and 5, the difference between Gonal-F and u-hFSH HP in terms of the number of oocytes retrieved and the number of embryos obtained did reach high levels of statistical significance. However, while the data did show a difference in the clinical pregnancy rate between Gonal-F and u-hFSH HP (ie Gonal-F demonstrated 22% more pregnancies per started cycle) - this difference did not reach statistical significance. Serono believed that the difference was strongly indicative of the clinical trend and that recombinant products were more bio-potent than urinary products. It was almost certain that, given the greater number of patients in the trial, the statistical significance would have been demonstrated in the case of clinical pregnancy rate. Serono considered it likely that differences in the pregnancy rates found in the trials would be considered clinically significant by most doctors.

Serono did not accept that the claim of "22% more pregnancies/start cycle" was exaggerated or unsubstantiated. The presentation of the findings made it clear which differences were statistically significant and which were trends, and the figures were derived from the clinical publication by Bergh.

In response to the allegation that use of the Bergh paper constituted unbalanced claims in view of the other available data on Gonal-F, Serono replied that this paper was the only comparative study of Gonal-F versus a currently available urinary FSH product. The only other data available on Gonal-F were old studies using comparators which were not presently marketed. Serono considered use of such out of date studies to be not relevant to prescribers.

#### PANEL RULING

The Panel considered that the layout of the pages with all but the bar chart in question showing statistically significant differences was such that readers would gain the impression that the 22% difference between Gonal-F and u-hFSH HP with regard to pregnancies per start cycle was statistically significant. This was not so. The Panel ruled that the claim was misleading as alleged in breach of Clause 7.2 of the Code. The Panel considered that its ruling of a breach of Clause 7.2 covered the allegation of a breach of Clause 7.8 and made no ruling in that regard.

The Panel also considered that the bar chart headed "Clinical Pregnancy Rate" was visually misleading, in breach of Clause 7.6 of the Code, as it gave the impression that there was a difference between the products and this was not borne out by the statistics. No such allegation had been made but the Panel requested that Serono be advised of its views in this regard.

The Panel noted Serono's submission that the Bergh paper was the only comparative study of Gonal-F versus a currently available urinary FSH product. The only other data available were old studies using comparators which were not presently marketed. Organon had not provided any material to support its allegation. The Panel therefore considered that in the circumstances it was not unreasonable to use the Bergh paper. No breach of Clause 7.2 of the Code was ruled.

### 4 Page 6 headed "Gonal-F improving the standard of effectiveness"

This page showed a chart comparing the benefits of Gonal-F to u-hFSH HP. With regard to pregnancy test, the chart in effect stated that "Higher Pregnancy rate per cycle" gave the opportunity for increased efficiency through improved effectiveness and increased value.

#### COMPLAINT

Organon alleged that Clause 7.2 of the Code had been violated blatantly by stating that a higher pregnancy rate was found, Serono could not claim an improved effectiveness or the heading "improving the standard of effectiveness".

#### RESPONSE

Serono said that it accepted that its claim "higher pregnancy rate per cycle" should not have been included on this page, and that this was contrary to Clause 7.2 of the Code. As mentioned above, it had discontinued this promotional item.

#### PANEL RULING

The Panel noted that the claim "Higher Pregnancy rate per cycle" was referenced to the Bergh study which had shown no statistically significant difference between Gonal-F and u-hFSH HP. The Panel ruled that the claim was misleading in breach of Clause 7.2 of the Code as acknowledged by Serono.

**Complaint received** 23 April 1998

**Case completed** 17 June 1998

CASE AUTH/702/4/98

*NO BREACH OF THE CODE*

# DIRECTOR/MEDIA v BIOGEN

## Media lunch

**An article by Dr James Le Fanu in the Sunday Telegraph was headed "Health" with the subheading "Dr James Le Fanu is wined and dined by a drug company but feels he must bite the hand that feeds him". De Le Fanu wrote in his article that he had been "... invited by the company Biogen to an extravagant lunch to promote its multiple sclerosis drug Avonex". In accordance with established procedure, the matter had been taken up as a complaint under the Code.**

**The Panel noted that the lunch in question had been held in association with a press briefing and that those invited had been journalists from both the lay media and the medical/pharmaceutical media. Dr James Le Fanu was medically qualified but he had been invited in his capacity as a journalist. The Panel considered that because the press briefing was concerned with the question of whether the present situation as regards the provision by the NHS of expensive medicines such as beta interferon was satisfactory, its aim was to try to obtain wider provision within the NHS, and thus greater sales. The event was promotional in nature, albeit indirectly, and therefore subject to the Code. Nonetheless, the Panel did not consider that the matter came within the scope of the provisions of the Code which concerned hospitality, as these related to hospitality to members of the health professions and appropriate administrative staff. The Panel considered that the subject matter of the briefing was not unreasonable and the cost of the lunch had not been excessive for this type of event. The Panel did not consider that the event had brought the industry into disrepute. It was ruled that there had been no breach of the Code.**

### COMPLAINT

This case arose from an article written by Dr James Le Fanu which appeared in the Sunday Telegraph on 26 April 1998. The article was headed "Health" with the subheading "Dr James Le Fanu is wined and dined by a drug company but feels he must bite the hand that feeds him". Dr Le Fanu wrote in his article that he had been ".... invited by the company Biogen to an extravagant lunch to promote its multiple sclerosis drug Avonex, whose generic name is beta interferon". In accordance with established procedure, the matter had been taken up as a complaint under the Code of Practice.

When writing to Biogen Limited the Authority drew attention to the provisions of Clauses 2 and 19 of the Code of Practice.

### RESPONSE

Biogen said that it had not violated the Code, in particular Clause 19, because the event in question was not a promotion of Avonex. The lunch, held on 2 April 1998, was for the purpose of presenting extensive information to the press regarding a matter of public policy in the UK: the refusal of many local health authorities to provide patients with proven therapies for the debilitating disease multiple sclerosis (MS), despite the NHS Executive's recommendation that any patient with MS who needed this type of treatment should have it funded. The attendees were not physicians who made prescribing decisions, but rather members of the press who would have an interest in this issue, including writers for the Sunday Telegraph (the sole medical doctor, invited in his capacity as a journalist), the Daily Mail, Scrip, and Economics, Medicines and Health. A neurologist gave a presentation concerning the incidence and effects of the disease and a speaker from a research organisation gave a presentation regarding how costs could affect the availability of MS therapies throughout Europe. Factual and balanced press materials were provided to attendees. Thus, the event did not constitute hospitality to members of the health professions under Clause 19.

Additionally, the event did not constitute excessive hospitality. It was Biogen's position that Clause 19 did not apply; however, the arrangements for the lunch were not excessive and certainly not of a nature to bring discredit upon the pharmaceutical industry. The venue was a restaurant in London. The cost of the food was £29 per person, the least expensive option. Details of the cost of the drinks were provided. Biogen considered that the food and drink were secondary to the purpose of the meeting, proportional to the event, and not beyond what a recipient would pay for himself (particularly in London). Because of Biogen's surprise at the substance of Dr Le Fanu's article, it had felt it appropriate to inform him of the cost per head. Dr Le Fanu responded that he would not wish his article to be seen as a criticism of Biogen, and that he would consider the £29 amount to be reasonable.

### PANEL RULING

The Panel noted that the lunch in question had been held in association with a press briefing and that those invited had been journalists from both the lay media and the medical/pharmaceutical media. Dr James Le Fanu was medically qualified but he had been invited in his capacity as a journalist. The Panel noted that a neurologist gave a presentation about MS and another presentation was given about how cost could affect the availability of MS therapies throughout Europe. The press materials included details about Avonex as well as other information. The Panel considered that because the press briefing was concerned with the question of whether the present situation as regards the provision by the NHS of expensive medicines such as beta interferon was satisfactory, its aim was to try to obtain wider provision within the NHS, and thus greater sales. The Panel considered that the event was promotional in nature, albeit indirectly, and therefore subject to the Code. Nonetheless, the Panel did not consider that the matter came within the scope of Clause 19 of the Code, which concerned hospitality to members of the health professions and appropriate administrative staff. The Panel therefore ruled that there had been no breach of that clause. The Panel considered however that

companies would be well advised to bear in mind the requirements of Clause 19 of the Code when arranging events for the media.

The Panel considered that in the circumstances the subject matter of the briefing was not unreasonable and the cost of the lunch had not been excessive for this type of event.

The Panel did not consider that the event had brought the industry into disrepute and accordingly ruled that it was not in breach of Clause 2.

**Proceedings commenced** **30 April 1998**

**Case completed** **18 June 1998**

---

**CASE AUTH/703/5/98**

# GLAXO WELLCOME v MERCK SHARP & DOHME

## Singulair detail aid

**Glaxo Wellcome complained about a Singulair detail aid issued by Merck Sharp & Dohme. The detail aid showed an artist's impression of airways inflamed in asthma before and after treatment with Singulair. The diameter of the open airway was 2.8cm and in the inflamed airway it was 0.6cm, representing nearly 80% occlusion. Glaxo Wellcome said that this might be consistent with severe inflamation but could not be substantiated by the data provided. It was alleged that the illustration was misleading. The Panel considered that readers would appreciate that the illustrations were schematic. The diagrams had not been made to resemble human lungs and knowledge of the true change in diameter was not available. In the Panel's view, the illustration showed a sequence of events and was not meant to demonstrate an absolute change in size. No breach of the Code was ruled. Upon appeal by Glaxo Wellcome, the Appeal Board considered that the illustration was misleading as it exaggerated the response to Singulair. This was not negated by the rider at the foot of the illustration that the "Illustration is an artistic rendition and does not necessarily reflect a level of change to be expected with medical therapy". It was an established principle that unacceptable material could not be qualified by the use of footnotes etc. A breach of the Code was ruled.**

**A bar chart headed "Significantly improved lung function" showed the mean percentage change from baseline for beclomethasone and beclomethasone plus Singulair in respect of $FEV_1$ (16 week average). The chart showed that the change with beclomethasone plus Singulair was statistically significant compared to beclomethasone alone. Glaxo Wellcome did not consider that a 5% improvment in $FEV_1$ related to a clinically significant improvement that a patient would find significant. In the Panel's view, there was sufficient information for the reader to assess the clinical significance of the data. The Panel noted the claim beneath the chart that significantly more physicians reported their patients improved versus beclomethasone alone. The Panel did not consider that the heading was ambiguous as alleged and no breach of the Code was ruled.**

Glaxo Wellcome UK Limited complained about a Singulair detail aid (ref: 1-99 SGA.97.GB/(W-6062) 13247.DA.10m.HO.198) issued by Merck Sharp & Dohme Limited.

### 1 Illustration of mode of action

#### COMPLAINT

Glaxo Wellcome noted that page 5 of the detail aid featured an artist's impression of airways that were inflamed in asthma before and after treatment with Singulair. The diameter of the open airway in this schematic illustration was 2.8cm and in the inflamed airway it was 0.6cm, representing nearly 80% occlusion. This might be consistent with severe inflammation but could not be substantiated by the data Merck Sharp & Dohme had provided nor by the claims below the illustration. Glaxo Wellcome alleged that the illustration was misleading in breach of Clause 7.6 of the Code.

#### RESPONSE

Merck Sharp & Dohme denied that the illustration exaggerated the response to leukotrienes. The company submitted that the illustration was clearly schematic. In the company's view physicians would be unlikely to be confused by this obvious artistic representation and, in any event, any possibility of confusion was negated by the unambiguous rider at the foot of the illustration "Illustration is an artistic rendition and does not necessarily reflect a level of change to be expected with medical therapy".

#### PANEL RULING

The Panel considered that readers would appreciate that the illustrations were schematic, particularly given the illustrations used to represent cysteinyl leukotrienes and Singulair.

The Panel noted its advice that airways of asthmatics were very sensitive and constricted or dilated on a regular basis within wide parameters. Further, the diagrams had not been made to resemble the human lung and knowledge of the true amount of physical change in diameter of airways was not available.

In the Panel's view, the illustration showed a sequence of events and was not meant to demonstrate an absolute change in size of airways. The Panel therefore ruled no breach of the Code.

#### APPEAL BY GLAXO WELLCOME

Glaxo Wellcome was surprised by the Panel's ruling and appealed strongly against this decision. Clause 7.6 of the Code clearly suggested that all artwork including illustrations, graphs and tables must conform to the letter and spirit of the Code. Graphs and table must be presented in such a way as to give a "clear, fair, balanced view of the matters with which they deal ...". The

supplementary information to Clause 7.6 stated "For example, anatomical drawings used to show results from a study must not exaggerate those results ...". Glaxo Wellcome strongly maintained that the illustration used clearly breached these requirements. The whole impact of the page was to suggest a substantial reduction in inflammation on receipt of Singulair. Although Glaxo Wellcome was quite well aware that this was an artistic representation and that there was a very small rider in the opposite page suggesting that the "Illustration is an artistic rendition and does not necessarily reflect a level of change to be expected with medical therapy", this did nothing to detract from the impact of the glossy illustration. Glaxo Wellcome would be wary about using such a dramatic depiction of this reduction in inflammation for any of its products and had chosen not to so do, as it considered it to be outside both the letter and the spirit of the Code.

## COMMENTS FROM MERCK SHARP & DOHME

Merck Sharp & Dohme expressed surprise at Glaxo Wellcome's response. Merck Sharp & Dohme repeated its submission that the illustration was clearly schematic, that physicians were unlikely to be confused by such an obvious artistic representation and in any event any possibility of such confusion was negated by the unambiguous rider at the foot of the illustration. Merck Sharp & Dohme endorsed the Panel's finding and the rationale given "... the illustrations were schematic particularly given the illustrations used to represent cysteinyl leukotrienes and Singulair", and also the Panel's observations on the fact that the diagrams had not been made to resemble the human lung.

Taking into account all the evidence and all the arguments raised at first instance, Merck Sharp & Dohme submitted that there was nothing to support the appeal.

In conclusion, Merck Sharp & Dohme reiterated its case that the diagram was clearly schematic and that there was no reasonable possibility of confusion as far as a physician was concerned. Merck Sharp & Dohme denied any breach of Clause 7.6.

## FURTHER COMMENTS FROM GLAXO WELLCOME

Glaxo Wellcome stated that the bright, colourful schematic representation of two airways was linked to the strapline "leukotrienes play a key role in asthmatic inflammation" and appeared on two pages sub-titled "Mode of Action". In the box adjacent to the representation of a very inflamed airway, Glaxo Wellcome would suggest severely inflamed, Merck Sharp & Dohme commented that cysteinyl leukotrienes bind to receptors to cause eosinophil recruitment, oedema, brocho-constriction and mucus secretion. In the schematic below, was the claim in the adjacent box that Singulair blocked the receptors to inhibit the actions of the cysteinyl leukotrienes. While Glaxo Wellcome was aware of the data suggesting that Singulair had weak bronchodilating activities and one study, as yet unpublished, showed a reduction in sputum eosinophils, it was not aware of any data published or on file to confirm that Singulair reduced oedema or mucus secretion. However, the two boxes and the diagrams adjacent clearly implied that these effects were seen with Singulair.

Glaxo Wellcome was still very strongly of the opinion that the artistic renditions exaggerated any effect that one would expect to see with a leukotriene receptor antagonist. Indeed, Merck Sharp & Dohme suggested that physicians were unlikely to be confused by such an obvious artistic representation. Merck Sharp & Dohme did not state it was impossible for such confusion to be created. It was Glaxo Wellcome's understanding after discussion with some respiratory physicians that confusion was indeed created by this schematic. Glaxo Wellcome understood that in a previous decision exaggerated visuals had been found to be in breach of Clause 7.6 of the Code. Glaxo Wellcome believed this in particular applied to some reproduced photographs of changes seen in blood vessel walls before and after treatment with an ACE inhibitor. Although these representations were actually based on real photographs, nevertheless they were considered to be in breach.

The airways in the Singulair detail aid were not based on actual pathological samples but were purely meant to be representative. Indeed Glaxo Wellcome, along with other companies working in the asthma arena, used similar visuals, but Glaxo Wellcome suggested that the upper visual was clearly that of a severely inflamed airway and the lower visual of a near normal airway. Glaxo Wellcome alleged that to create this impression and suggest that such change, such improvement, was possible with Singulair treatment was not capable of substantiation at this stage. Indeed Glaxo Wellcome considered that such a dramatic response to any single agent could not be irrevocably demonstrated and it was still firmly of the view therefore that this represented an exaggerated claim in breach of the Code.

Glaxo Wellcome referred to the use of the rider by Merck Sharp & Dohme. The view of Merck Sharp & Dohme was that the artistic impression did need to be negated by an unambiguous rider. Merck Sharp & Dohme had suggested that this was at the foot of the illustration, yet the glossy picture covered two pages of the detail aid. The airways with the respective boxes appeared at the far right hand side, while the rider, in very small white print on a light blue background, appeared at the far left hand side of the left hand page. Glaxo Wellcome believed that this rider should be made much stronger, much bolder and should appear adjacent to the two diagrams to fulfil Merck Sharp & Dohme's wish that it negated any confusion. It was Glaxo Wellcome's understanding that the Panel also considered that such riders and disclaimers should appear close to where the impression was being created.

## APPEAL BOARD RULING

The Appeal Board considered that the illustration was misleading as it exaggerated the response to Singulair. This was not negated by the use of the rider. It was an established principle that unacceptable material could not be qualified by the use of footnotes etc. The Appeal Board ruled a breach of Clause 7.6 of the Code.

The complainant's appeal was successful.

### 2 Bar chart headed "Significantly improved lung function"

Page 9 of the detail aid included a bar chart headed "Significantly improved lung function". The bar chart showed the mean percentage change from baseline for beclomethasone and beclomethasone plus Singulair in respect to $FEV_1$ (16 week average). The bar chart showed that the change with beclomethasone plus Singulair was statistically significant compared to beclomethasone alone ($p<0.05$).

#### COMPLAINT

Glaxo Wellcome had asked Merck Sharp & Dohme to clarify the claim to read "Statistically significantly improved lung function". Merck Sharp & Dohme had declined to do so suggesting that it was quite clear that the bar chart implied that it was only statistical significance that was being claimed.

Glaxo Wellcome strongly disagreed that a 5% improvement in FEV1 over beclomethasone alone related to a clinically significant improvement that a patient would find significant. This had been the subject of correspondence between the companies. Glaxo Wellcome alleged that the heading was ambiguous in breach of Clause 7.2 of the Code.

#### RESPONSE

Merck Sharp & Dohme pointed out that Singulair was licensed as an add on treatment to inhaled corticosteroids for the management of asthma. The pivotal trial for the indication was study 029, a summary of which was provided. The data in the detail aid was directly derived from this pivotal study. Merck Sharp & Dohme stated that by implication Glaxo Wellcome would appear to be calling into question the validity of the licence which was granted by the Medicines Control Agency. The assertion of statistical significance was axiomatic as that difference was proven. As regards the assertion of "clinical significance", this by its nature was subjective in basis. Merck Sharp & Dohme submitted that the inference was supported by the second bullet point where the physicians had made a clinical judgement and observed in their opinion the patient symptoms had improved and this observation itself had statistical significance. It was therefore clear that Glaxo Wellcome's concern that the 5% improvement was not clinically significant was not warranted.

#### PANEL RULING

The Panel noted that there was a statistically significant difference in favour of beclomethasone plus Singulair compared to beclomethasone alone. The bar chart showed average $FEV_1$ over a 16 week period. The figure $p<0.05$ was given next to the bar chart.

In the Panel's view there was sufficient information for the reader to assess the clinical significance of the data. It was clearly statistically significant and had been derived from a 16 week study. The Panel noted the claim below the bar chart that significantly more physicians reported their patients improved ($p=0.001$ versus beclomethasone alone). The Panel did not accept that the heading to the bar chart was ambiguous as alleged. No breach of Clause 7.2 of the Code was ruled.

**Complaint received** **8 May 1998**

**Case completed** **18 August 1998**

CASE AUTH/704/5/98

*NO BREACH OF THE CODE*

# HOSPITAL PHARMACIST v LEO

## Innohep advertisement

**A hospital formulary pharmacist alleged that Leo's advertisement for Innohep (a low molecular weight heparin), and its associated prescribing information, were misleading. It was claimed in the advertisement, and stated in the prescribing information under "Dosage and Administration", that no laboratory monitoring was required. Conversely a recent independent review on the therapy area had stated that full blood counts should be done to detect the possible development of thrombocytopenia. It was also alleged that the term "monitoring" had been incorrectly used as it included monitoring for efficacy and adverse events.**

**The Panel noted that the Innohep summary of product characteristics (SPC), under "Posology and Method of Administration", stated that "There is no need to monitor Innohep treatment" and under "Undesirable Effects" stated that thrombocytopenia may occur rarely but was silent on the need to monitor for its development. The prescribing information thus reflected the SPC and was not misleading. No breach of the Code was ruled.**

**In the Panel's view the thrust of the advertisement was the ease of administration of Innohep in terms of dosage, frequency of dosage and availability of dosage forms. Given the context of the advertisement the Panel considered that the claim "No laboratory monitoring required" was not unacceptable. No breach of the Code was ruled.**

A hospital formulary pharmacist complained about an advertisement for Innohep (tinzaparin) issued by Leo Pharmaceuticals. The advertisement had appeared in the British Medical Journal, 25 April 1998.

### COMPLAINT

The complainant noted that the advertisement claimed that no laboratory monitoring was required. This was not the case. As the recent Drug and Therapeutics Bulletin stated (Vol 36 No 4 April 1998), platelets must be monitored via a full blood count on the 4th to 6th day of treatment as the incidence of thrombocytopenia was not yet known. Thus the advertisement was misleading and the abridged data sheet included on the page was also misleading. The term "monitoring" included monitoring for efficacy and adverse effects. Therefore it had been incorrectly used in this situation.

### RESPONSE

Leo stated that the claim "No laboratory monitoring is required" was a variation of the statement "There is no need to monitor the Innohep treatment" which appeared in the UK product licence for Innohep, the summary of product characteristics (SPC) and also in the dosage and administration section of the prescribing information.

Leo noted that the Drug and Therapeutics Bulletin was independently written and the article referred to by the complainant reflected the personal views of the author.

Leo noted the allegation that the abridged data sheet included on the page was misleading. Leo stated that the information on the advertisement succinctly listed the full SPC for Innohep and was not an abridged version as stated by the complainant.

In conclusion, Leo considered that the advertisement in question was a clear representation of the UK product licence and SPC for Innohep and, as such, was not misleading and did not contravene Clause 7 of the Code.

### PANEL RULING

The Panel noted that the Drug and Therapeutics Bulletin referred to by the complainant contained a five page review on low molecular weight heparins for venous thromboembolism. Within the section detailing unwanted effects there was a paragraph on thrombocytopenia. Because of the possibility of thrombocytopenia developing the advice given was that "... in any patient receiving [a low molecular weight heparin] ... a full blood count should be done on the 4th-6th day of treatment ...". The Panel noted that the Drug and Therapeutics Bulletin was described as "The independent review for doctors and pharmacists from Consumers' Association.".

The Panel noted that section 4.2 of the Innohep SPC (Posology and Method of Administration) stated "There is no need to monitor the Innohep treatment". The Panel noted that the prescribing information given in the advertisement reflected the SPC. It also stated, under "Dosage and Administration", that there was no need to monitor Innohep treatment.

In section 4.8 of the SPC (Undesirable Effects) it was stated that thrombocytopenia may occur rarely. The Panel noted that one of the contra-indications to Innohep therapy was thrombocytopenia in patients with a positive *in vitro* aggregation test in the presence of tinzaparin. The Panel considered that it might be prudent to monitor for thrombocytopenia but noted that such a requirement was not expressly stated in the SPC. Conversely the SPC did not state that there was no need to monitor for thrombocytopenia. The Panel noted that the prescribing information in the advertisement reflected the SPC with regard to thrombocytopenia.

The Panel noted that the claim in question was one of five stab points which appeared in the advertisement. In the Panel's view the thrust of the advertisement was the ease of administration of Innohep in terms of dosage, frequency of dosage and availability of dosage forms. The Panel considered that in the context of the advertisement the claim "No laboratory monitoring required" was not unacceptable. No breach of Clause 7.2 was ruled. The Panel considered that the prescribing information was not misleading as alleged and no breach of Clause 7.2 was ruled.

**Complaint received** 8 May 1998

**Case completed** 6 July 1998

CASE AUTH/705/5/98

*NO BREACH OF THE CODE*

# PRACTICE SERVICES MANAGER v TRINITY

## Conduct of a representative

**A practice services manager complained about the conduct of a representative from Trinity. It was alleged that the representative had told her that he had been asked by the pharmaceutical adviser at the local health authority to contact practices in the area with a view to changing repeat prescriptions on the computer system from generic, or other branded products, to Trinity products in order to cut prescribing costs. The practice had only recently carried out this exercise in conjunction with the health authority. The complainant had telephoned the pharmaceutical adviser who confirmed that, whilst he had spoken to the representative, he had certainly not asked him to contact practices.**

**The Panel noted that the parties had provided differing accounts of the conversation between the representative and the complainant. It was difficult in such cases to determine what had transpired. There were two pharmaceutical advisers at the health authority. The complainant had talked to the first one and the representative, apart from a brief telephone conversation with the first, had mainly talked to the second. There might have been some confusion because their names were similar. Trinity had said that it was the second adviser who had asked the representative to contact practices. The Panel considered it unfortunate that the representative had left the impression that he had been asked to change computerised repeat prescriptions. However, given the parties' differing accounts of the conversation the Panel was not in a position to determine precisely what had been said. No breach of the Code was ruled.**

A practice services manager complained about the conduct of a representative from Trinity Pharmaceuticals Ltd.

### COMPLAINT

The complainant stated that the representative had visited the surgery (cold call) and asked to see the complainant with a view to reducing the practice's prescribing costs. The complainant stated that the representative informed her that he had been asked to contact practices in the area by the pharmaceutical adviser at the local health authority with a view to changing repeat prescriptions on the computer system from generic, or other branded products, to Trinity products in order to cut prescribing costs.

As the practice had only very recently completed this exercise in conjunction with the health authority, and with approval from the patients concerned, the complainant thought this rather odd and commented on this. The representative then went on to say that the pharmaceutical assistant who had undertaken the work had "missed some" so the pharmaceutical adviser had asked him to chase up those medicines that had been missed. Again the complainant was suspicious as the pharmaceutical assistant was a very bright, fully qualified pharmacist. The representative had also stated that the health authority should have given him a list of those practices which had already undergone the health authority review and then asked if the complainant's practice was the only practice in the area.

The complainant was also informed that Trinity would pay for staff time taken to change patients' computer generated repeat prescriptions.

The complainant asked the representative if he had a business card but was informed that he had just given his last one out. The complainant took careful note of his name and mobile telephone number and the representative said that he would contact the complainant again in approximately two weeks' time to give the complainant time to arrange the necessary computer searches.

Feeling quite sure that the health authority had no involvement, the complainant telephoned the pharmaceutical adviser who confirmed that, whilst he had spoken to the representative on the telephone, he had certainly not asked him to contact practices, nor had his assistant missed any drugs in the exercise recently undertaken. The pharmaceutical adviser was going to write to other practices in the area to bring this to their attention.

### RESPONSE

Trinity stated that the representative was adamant that he had in no way sought to mislead the complainant and indeed he left the meeting with the impression that he had agreed a repeat call in two weeks' time. The company was thus concerned that the complainant did not make her concerns known to the representative during the meeting. He in no way sought to hide his identity and willingly provided his name, company and telephone number in the absence of a business card. Trinity found it disturbing that the complainant had made an issue over the fact that the representative did not have a business card. This, although regrettable, happened not infrequently to people who carried/used business cards.

Trinity stated that with regard to the involvement of health authority staff it appeared that the representative had had a very brief telephone conversation with the pharmaceutical adviser who referred him to a colleague who was also a pharmaceutical adviser for the health authority. It was this second pharmaceutical adviser who, following discussions with the representative, suggested that the representative might usefully follow-up on the work of one of his colleagues since she (his colleague) was probably not aware of the cost savings offered by Trinity and might therefore have missed a number of opportunities. This discussion appeared to have upset (or confused) the complainant although this was not the representative's intention. However, the representative and Trinity were more than happy to apologise for any upset that might have been caused.

Trinity stated that, regarding the issue of the representative offering to help with the costs associated with transferring computer generated repeat

prescriptions, large practices who agreed with the cost savings to be offered by Trinity brands could be faced with a considerable extra administrative burden to alter computer records for repeat prescriptions. In such instances Trinity considered it to be a legitimate business practice to offer assistance with this task including the reimbursement of directly attributable out of pocket expenses incurred by the practice (such as overtime hours taken by practice staff).

Trinity submitted that the complaint appeared to be the result of an enthusiastic sales representative rather than any deliberate attempt to mislead or misrepresent the facts.

Trinity confirmed that other than a brief telephone conversation between the representative and the first pharmaceutical adviser, it did not have a relationship with the first pharmaceutical adviser.

Trinity provided the Panel with a copy of the representative's response to the complaint. The representative stated that he introduced himself to the complainant and explained the Trinity concept to her. The complainant informed the representative that the practice had recently had a pharmaceutical adviser helping with prescribing costs.

The representative stated that he was aware that a pharmaceutical adviser was in the process of dealing with practices in the area as he had recently spoken to the second pharmaceutical adviser for the health authority. It was at this point that the representative told the complainant about his conversation with the second pharmaceutical adviser where the pharmaceutical adviser explained that he had a female colleague working in the same area who was probably not aware of Trinity and its cost saving concept and it might therefore be useful to the representative to have a list of practices she had recently visited in order that he might be able to offer further cost savings in modified release only. The representative had tried on one occasion to follow up the second pharmaceutical adviser's offer but had been unable to contact him. The representative stated that he did not at any point mention the first pharmaceutical adviser as he had only ever had a brief conversation with him, and it was at his suggestion that the representative dealt with the second pharmaceutical adviser.

The representative stated that throughout his conversation with the complainant he had remained professional, fully explaining his role as a Trinity representative within the cost saving process. The representative was aware that it was not company or industry policy to offer any financial inducements, although he did sympathise with the complainant with regard to the staff costs and time taken to undertake a drug audit. This conversation reached the natural conclusion that the effort applied now would ultimately save money for the practice. The complainant then agreed to undertake a drug audit which the representative agreed to collect in two weeks.

## FURTHER COMMENTS FROM THE COMPLAINANT

The complainant, having read Trinity's response, confirmed that the representative had not tried to hide his identity; the matter of the business card was not an issue. The complainant had asked for his card to ensure that she had the correct details of the representative and his company. Nor was she complaining about assistance with staff costs.

The complaint was based purely around the fact that the representative had deliberately tried to mislead by stating that the health authority had actually asked him to contact practices with a view to changing computerised repeat prescriptions to Trinity products. When the complainant "tested" his statement by telling him that the practice had just completed a review with the direct assistance of a health authority medical adviser he again tried to deliberately mislead by saying that she had missed some and he had been asked to check up on these. The complainant alleged that this was a deliberate lie to try to cover his tracks. The complainant therefore disputed the claim that the tactics were merely enthusiastic.

## PANEL RULING

The Panel noted that the parties had provided differing accounts of the conversation between the representative and the complainant. It was difficult in such cases to determine exactly what had transpired. A judgement had to be made on the available evidence. The Panel noted that according to the accounts of the complainant and the representative, there were two pharmaceutical advisers to the health authority. The complainant had talked to the first one whilst the representative, apart from a brief telephone conversation with the first, had mainly talked to the second.

The Panel examined the statement made by the representative. The representative stated that he had spoken to the second pharmaceutical adviser to the health authority who had mentioned a female colleague working in the area who was probably not aware of Trinity. The pharmaceutical adviser had said that it would be useful to the representative to have a list of the practices that his colleague had recently visited so that the representative might offer further cost savings in "modified release only". The Panel noted that the representative had attempted to speak to the second pharmaceutical adviser on one further occasion to discuss his offer but had been unable to contact him. The Panel noted that the representative stated that he had not at any point in the meeting with the complainant mentioned the first pharmaceutical adviser as the representative had only ever had a brief telephone conversation with him.

The Panel noted that whilst it was not necessarily a breach of the Code for a representative to liaise with a general practice to effect a computer generated product switch, all of the arrangements had to comply with the Code and companies and their representatives should be careful about the methods employed. Any payments needed to comply with the provisions of Clause 18.1 of the Code.

The Panel noted that the complainant had specifically stated in her comments on Trinity's response to her complaint that she was not complaining about the provision of assistance with staff costs. It was accordingly not for the Panel to rule upon this aspect of the matter and the Panel decided not to take the matter up under

Paragraph 16 of the Constitution and Procedure because it was not clear exactly what had happened in the present case. Nonetheless, the Panel was concerned to note that the company had stated that it saw the reimbursement of directly attributable out-of-pocket expenses incurred by a practice when altering computer records as being a legitimate business practice. The Panel could see little difference in principle between this situation and that in a recent case (Case AUTH/689/3/98) in which a company had been ruled in breach of Clause 18.1 of the Code for providing finance to a health authority so that the health authority could reimburse costs incurred by practices when considering switching patients from a competitor's product to that of the donor company. The Panel agreed that this should be drawn to Trinity's attention.

The Panel noted that the complainant was under the impression that the first pharmaceutical adviser had asked the representative to contact practices. Trinity had stated that it was the second pharmaceutical adviser who had suggested this. The further comments from the complainant stated that the representative had been asked by the health authority to contact practices with a view to changing computerised repeat prescribing. The Panel considered that it was unfortunate that the representative had left that impression with the complainant. The Panel noted that the representative had had a telephone conversation with health authority staff and there might have been some confusion due to the similarity of the two pharmaceutical advisers' names and the fact that they had the same job title.

The Panel bore in mind that extreme dissatisfaction was necessary on the part of a complainant before he or she was moved to submit a complaint. However, given the parties' differing accounts of the conversation the Panel was not in a position to determine precisely what had been said. The Panel therefore ruled no breach of Clause 15.2 of the Code.

**Complaint received** **12 May 1998**

**Case completed** **29 July 1998**

---

**CASE AUTH/707/5/98**

# DIRECTOR OF PHARMACY SERVICES v KNOLL

## Conduct of a representative

**A director of pharmacy services complained about the conduct of a representative from Knoll. The complainant stated that the representative had accused the hospital of using lansoprazole in preference to pantoprazole as a "loss leader". The complainant alleged that this was incorrect and highly unprofessional and appalling practice.**

**The Panel noted that Knoll had not disputed the complainant's allegation and that the remark was incorrect and unprofessional. The company had accepted responsibility and introduced procedures to avoid a similar incident in the future. The Panel considered that the representative had failed to maintain a high standard of ethical conduct and a breach of the Code was ruled.**

### COMPLAINT

A director of pharmacy services at a hospital complained about the conduct of a representative from Knoll Limited.

The complainant stated that he had visited a GP practice to talk about pharmaceutical problems arising around the primary/secondary care interface. One problem raised was that of using "loss leaders". This was a practice the hospital had avoided for some fifteen years through careful scientific evaluation of products through the Drugs and Therapeutics Committee and having a GP member of the Committee. It was therefore of great concern to the complainant to learn that the Knoll representative for the area had accused the hospital of using lansoprazole in preference to pantoprazole (Knoll's product, Protium) in this manner. As well as being incorrect, the complainant considered it was highly unprofessional and appalling practice.

The complainant had written directly to Knoll and copied the letter to the Authority.

### RESPONSE

Knoll established that the representative in question had only joined the company in April 1998. So far he had only received limited induction training pending his joining the full course for new joiners which would begin in June. He had passed the ABPI representatives examination.

It would appear that the representative did allow himself a speculative remark to the GP involved, about price levels in hospitals and Knoll accepted responsibility for the remark. The representative would receive the appropriate counselling and as a second step the company would henceforward include in its training programme an item which expressly required representatives to avoid discussions on hospital pricing at the primary care interface. The second point arose out of a suggestion made by the complainant.

The complainant questioned the ethos of Knoll in the matter of "loss leaders". The company strongly denied encouraging or indeed condoning any communications of this nature: it recognised only too well that it was not the role of the industry to make assumptions about hospital policy and air such theories in the arena of primary care. This sentiment had been conveyed to the complainant in the sincerest possible terms.

Knoll supplied copies of new joining and training guidelines for representatives joining Knoll Limited. The guidelines stated there would a set of joining and induction days throughout the year and no representative should be brought into the company on any other occasion. No unaccompanied calls should be made prior to full training. The company provided a copy of the record card for the visit with the general practitioner

together with details of the Protium induction training. The company had sent these documents to the complainant.

### PANEL RULING

The Panel noted Clause 15.10 of the Code stated that companies were responsible for the activities of their representatives if these were within the scope of their employment.

The Panel noted the complainant's allegation that the remark was incorrect and unprofessional. This was not disputed by Knoll which acknowledged that the representative had made a speculative remark to a GP about price levels in hospitals. Knoll accepted responsibility for the remark and had introduced procedures to avoid a similar incident in the future. The Panel noted the complainant's comment that the hospital avoided the practice of loss leaders by careful scientific evaluation. In the circumstances the Panel considered that the representative had failed to maintain a high standard of ethical conduct and a breach of Clause 15.2 of the Code was ruled.

**Complaint received** **15 May 1998**

**Case completed** **1 July 1998**

---

**CASE AUTH/708/5/98** *NO BREACH OF THE CODE*

# GENERAL PRACTITIONER v MERCK SHARP & DOHME

## Innovace Melt mailing

**A general practitioner complained about a mailing for Innovace Melt sent by Merck Sharp & Dohme. The mailing consisted of a square cardboard package inside which was a hexagonal sealed foil wrapper containing a leaflet about Innovace Melt. The mailing was based on the theme of taste. The complainant alleged that the advertising was anything but the best possible taste and the packaging was extremely expensive.**

**The Panel noted Merck Sharp & Dohme's submission that the hexagonal wrapper had been designed to resemble the shape and packaging of Innovace Melt. The Panel noted the estimated cost of production, excluding postage, was 24 pence per item which, in the Panel's view, was not excessive. The Panel considered that the mailing was not likely to cause offence and nor had the company failed to maintain high standards. The Panel therefore ruled no breach of the Code.**

A general practitioner submitted a complaint about a mailing for Innovace Melt (ref: 01-99 RNT.97.GB.20327.M.44m.QO.198) sent by Merck Sharp & Dohme Limited.

The mailing consisted of a square cardboard package with, on one side, the statement "All in the best possible ..." and illustrations of household items that might be considered to be of questionable taste. Inside the package was a hexagonal sealed foil wrapper containing a leaflet about Innovace Melt. The illustrations on the front and back cover of the leaflet continued the theme of taste.

### COMPLAINT

The complainant found it particularly annoyingly ironic that the outside of the package stated "All in the best possible ...", assuming that one would add "taste". He found this form of advertising anything but the best possible taste. The packaging was obviously extremely expensive, being a large silver foil case inside a cardboard box, which in the end revealed a hexagonal colour leaflet on a new formulation of enalapril maleate, Innovace.

The complainant was not sure this form of advertising fell within the normal bounds of appropriateness, and whether or not the company was in breach of the Code. Undoubtedly, however, it was a rank waste of money. The complainant thought there was very good evidence that cold mailing of information to GPs very rarely, if ever, changed prescribing habits, and although he was aware that a company was obliged to send a copy of data sheet information when a new product or indication or licence change occurred, he was sure it would be much better if this was done by the ABPI in the form of a standard handout based on some form of ring binder such that practices could keep up to date whilst waiting for the next edition of the ABPI Compendium of Data Sheets and Summaries of Product Characteristics. The complainant suggested that the ABPI publish the compendium with some blank pockets or clip-in device at one end.

* * *

The Authority had advised the complainant that it was not unacceptable per se to mail promotional material to health professionals. The complainant could ask to have his details removed from the mailing list. The Authority also pointed out that pharmaceutical companies were not required to send summaries of product characteristics to doctors and dentists prior to advertising. The comments about the format of the Compendium were referred to the ABPI.

* * *

### RESPONSE

Merck Sharp & Dohme was sorry that the general practitioner had considered it necessary to complain but did not believe that the mailing breached the Code.

Whilst the mailing had been specially commissioned to resemble the Innovace Melt medicine - hexagonal, foil wrapped - it was certainly no more costly than any high quality mailing appropriate to the medical profession. The estimated cost of production was 24 pence per item, excluding postage.

Merck Sharp & Dohme submitted that the mailing was entirely appropriate as this new formulation of Innovace offered additional benefits and might aid patient

compliance, which was particularly important for the treatment of an asymptomatic condition.

### PANEL RULING

The Panel noted the company's submission that the hexagonal foil wrapper had been designed to resemble the shape and packaging of Innovace Melt. The leaflet gave information about the introduction of Innovace Melt.

The Panel noted the requirements of Clause 9.6 of the Code that extremes of format, size or cost of promotional material must be avoided. It noted that the estimated cost of production, excluding postage, was 24 pence per item which in the Panel's view was not excessive. The Panel ruled no breach of Clause 9.6. The Panel considered that the mailing was not unreasonable in relation to the requirements of Clause 9.1 of the Code which stated that material must not be likely to cause offence and that high standards must be maintained. The Panel therefore ruled no breach of Clause 9.1 of the Code.

**Complaint received** **15 May 1998**

**Case completed** **23 June 1998**

---

**CASE AUTH/709/5/98**

# DIRECTOR v SCHERING-PLOUGH

## Failure to comply with an undertaking

**An allegation from UCB Pharma that Schering-Plough was continuing to use a leavepiece which had previously been ruled to be in breach of the Code was taken up as a complaint by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. The claim "Depend on the world's leading antihistamine" in a Clarityn leavepiece had earlier been ruled to be a claim for a special merit which had not been substantiated.**

**The Panel noted that the company's representatives had been verbally instructed to cease using the leavepiece but written instructions had been issued only after the current allegation had arisen. The company had taken some action to comply with its undertaking but representatives had continued to use the material. The company had failed to comply with its undertaking and was ruled in breach. The Panel considered that the company's failure to comply with its undertaking brought discredit upon and reduced confidence in the pharmaceutical industry and ruled that there had also been a breach of Clause 2 of the Code. It was also decided to report Schering-Plough to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.**

**Upon appeal by Schering-Plough of the ruling of a breach of Clause 2, the Appeal Board considered that the procedures within Schering-Plough regarding the withdrawal of the material had been inadequate. The company should have issued detailed written instructions to ensure compliance with the undertaking. It was not sufficient to issue only verbal instructions. The company had failed to comply with the undertaking and this brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board ruled a breach of Clause 2 of the Code and the appeal therefore failed.**

**In relation to the report made by the Panel, the Appeal Board decided that, in accordance with Paragraph 10.4 of the Constitution and Procedure, Schering-Plough should be required to undergo an audit by the Authority of its procedures relating to the Code of Practice.**

**The Appeal Board subsequently considered the audit report and its recommendations. The Appeal Board's view was that Schering-Plough should implement the recommendations made in the report and on that basis no further action was necessary.**

### COMPLAINT

UCB Pharma Limited complained that Schering-Plough was continuing to use a Clarityn leavepiece which included the claim "Depend on the world's leading antihistamine". The claim had previously been ruled to be a claim for a special merit which had not been substantiated in breach of Clause 7.8 of the Code (Case AUTH/575/7/97).

UCB Pharma stated that the leavepiece had been distributed at a medical dinner dance which had been attended by two representatives from Schering-Plough.

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

### RESPONSE

Schering-Plough stated that the leavepiece was on display on its exhibition stand at a meeting for general practitioners and hospital doctors held on 8 May 1998. The company provided details about the event which had been organised by a general practitioner. The primary purpose of the meeting was medical education. Schering-Plough and eleven other pharmaceutical companies had sponsored the event. Promotion in the form of exhibition stands took place in a separate room to which only GPs and hospital medical staff had access.

The company had briefed its sales team to use only newly approved material on 11 September 1997. Despite the briefing the old leavepiece appeared to have been used in error and contrary to the company's instructions. The company wished to assure the Authority that all the material bearing the claim "Depend on the world's leading antihistamine" had been withdrawn in accordance with its undertaking and ruling of 7 November 1997. The sales representatives who improperly used the withdrawn materials had been disciplined appropriately and the company's procedures were being tightened to ensure that such an occurrence could not be repeated.

Schering-Plough provided a copy of a memorandum from the GP Business Unit Director to representatives and others. The memorandum dated 1 June 1998 reminded recipients that only current approved promotional material should be used. Further that specifically, all old Clarityn dosage cards with the wording "the world's leading antihistamine" should be destroyed. A copy of the Clarityn briefing document, Cycle III 1997, was also provided.

The company stated that the briefing not to use the promotional material in question had been a verbal briefing given at the national sales conference.

## PANEL RULING

The Panel noted that the company representatives had been verbally instructed to cease using the leavepiece. The only written instructions had been issued on 1 June 1998 which was after Schering-Plough had been notified of the complaint.

The Panel noted that the company had taken some action to comply with the undertaking but the representatives had continued to distribute material that had been ruled in breach of the Code. The company had therefore failed to comply with its undertaking. The Panel ruled a breach of Clause 21 of the Code.

The Panel considered whether there had also been a breach of Clause 2 of the Code in view of the fact that the continued use of the leavepiece represented a failure to comply with the undertaking and assurance previously given. The company had to take responsibility for the failure of representatives to withdraw the material. The Panel was concerned that the only instructions to representatives had been verbal. In the Panel's view this was not adequate. Companies should issue detailed written instructions to relevant staff about the action required to ensure compliance with undertakings. The Panel decided that the company's failure to comply with the undertaking brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was ruled. It was also decided to report Schering-Plough to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The question of the sponsorship of the medical dinner dance had been taken up with Schering-Plough under the provisions of Paragraph 16 of the Constitution and Procedure (Case AUTH/732/6/98).

## APPEAL BY SCHERING-PLOUGH

Schering-Plough submitted that the company should not be found in breach of Clause 2 of Code based on the inadvertent use of withdrawn promotional materials by its representative. The company was aware that a breach of Clause 2 might be found for failure to comply with an undertaking; however, there was case precedent involving human error to which Clause 2 was not applied. The company hoped to demonstrate that Clause 2 should not be applied to the present situation.

Schering-Plough noted that the Panel and the Appeal Board had found in the past that Clause 2 might not be appropriate where the use of withdrawn materials and resulting breach of an undertaking were due to human error, rather than an intention to violate the undertaking. In Case AUTH/182/7/94, the company had instructed its representatives in a sales force meeting to cease using certain claims found in breach of the Code; however, a representative erroneously used a standardised follow-up letter containing the claims. The company had accepted that the undertaking had been breached and tightened its policies, but appealed the imposition of Clause 2. The Appeal Board ruled that Clause 2 should not be applied because the breach was due to human error, even though the representative and the company's head office had contributed to the oversight. In another case (Case AUTH/31/4/93), the company failed to destroy an exhibition panel containing claims found in breach of the Code. By human error, it was subsequently displayed. Acknowledging that the company had taken steps to implement its undertaking and provided assurances that the use was in error, the Panel found no breach of Clause 2.

Schering-Plough submitted that the present case closely resembled precedent in which Clause 2 was not applied for the following reasons. Schering-Plough took steps to withdraw the materials that it believed in good faith at the time to be adequate under the guidelines on company procedures relating to the Code. Its advertisement bearing the claim "Depend on the world's leading antihistamine", the subject of the complaint, was promptly withdrawn in November 1997, following the Panel's ruling. Moreover, the company had already reissued new material, replacing the "old" material in September 1997. The company referred to the Clarityn conference briefing material previously supplied which was dated September 1997.

Schering-Plough stated that despite its efforts to ensure that the materials were not used again, a representative erroneously distributed them at one meeting. Appropriate disciplinary measures had been taken with respect to the personnel involved. The company recognised that a breach of an undertaking was a very serious matter. The breach of Clause 21 was not disputed because the company accepted fully that it was responsible for its representatives even if they acted contrary to instructions. Furthermore, unlike recent cases in which Clause 2 was applied, Schering-Plough did not delay in issuing its instructions for withdrawal of the materials, nor did it continue to supply them after the withdrawal.

Schering-Plough hoped that the Appeal Board would consider that it had taken action to prevent this situation from recurring, including reclarification to all sales personnel on withdrawal of the material on 1 June 1998. In light of the company's past efforts to comply with Code, the human error that caused this breach, and the company's renewed commitment to ensuring compliance with the Code, Schering-Plough hoped that the Appeal Board would agree that a ruling of a breach of Clause 2 was not necessary.

## APPEAL BOARD RULING

The Appeal Board considered that an undertaking was an important document. It required companies to provide details of the action taken and the date of final use of materials ruled in breach. The form of undertaking was to be signed by the chief executive or with his or her

authority. It included a section in which an assurance was given that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied promptly with undertakings given in relation to rulings under the Code. Companies should have procedures in place to ensure prompt compliance with undertakings. In the Appeal Board's view, companies would be well advised to issue detailed written instructions to relevant staff about the action required to ensure compliance with undertakings.

The Appeal Board considered that the procedures within Schering-Plough regarding the withdrawal of the material had been inadequate. The company should have issued detailed written instructions to ensure compliance with the undertaking. It was not sufficient to issue only verbal instructions. The company had failed to comply with the undertaking and this brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board ruled a breach of Clause 2 of the Code.

The appeal therefore failed.

## REPORT FROM THE PANEL TO THE APPEAL BOARD

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

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

## FINAL CONSIDERATION BY APPEAL BOARD

The Appeal Board subsequently considered the audit report and its recommendations. The Appeal Board's view was that Schering-Plough should implement the recommendations made in the report and on that basis no further action was necessary.

| | |
|---|---|
| **Proceedings commenced** | **18 May 1998** |
| **Appeal Board consideration of appeal and Panel's report** | **30 July 1998** |
| **Undertaking received** | **19 August 1998** |
| **Final consideration by Appeal Board** | **22 October 1998** |

CASE AUTH/710/5/98

# GLAXO WELLCOME v MERCK SHARP & DOHME

## Singulair advertisement on MIMS

**Glaxo Wellcome complained about a Singulair advertisement issued by Merck Sharp & Dohme. The advertisement which was in the form of an abbreviated advertisement appeared in a format similar to a "post-it note" and was stuck on the front cover of MIMS. Glaxo Wellcome alleged that as the advertisement was not firmly attached it should have included the full prescribing information.**

**The Panel's view was that the advertisement had to be considered as a loose insert, not bound in or permanently fixed in some way. The Panel considered therefore that the advertisement could not be an abbreviated advertisement and as the prescribing information had not been included a breach of the Code was ruled.**

Glaxo Wellcome UK Limited complained about a Singulair advertisement (ref 1-99 SGA.97.GB.13187.J.43m.CW.0398) issued by Merck Sharp & Dohme Limited. The advertisement appeared in a format similar to a "post-it note" and was stuck on the front cover of MIMS, April 1998.

### COMPLAINT

Glaxo Wellcome alleged that as the advertisement was not firmly attached to the journal it should have been regarded as a stand alone advertisement and not as an abbreviated advertisement. This being the case the full prescribing information should have been included. This had not been included and Glaxo Wellcome alleged a breach of Clause 4.1 of the Code.

### RESPONSE

Merck Sharp & Dohme submitted that it understood that the advertisement was firmly affixed to the front cover of MIMS, April 1998. It could therefore legitimately be treated as an abbreviated advertisement, within the exemptions of the requirement for prescribing information, as set out in Clause 5.1 of the Code.

The company submitted that it was not its intention that the advertisement should be considered a separate item, it was the company's understanding that it would form an integral part of the journal. The company denied any breach on this occasion but accepted that there was a possibility of such items being inadvertently separated from the journal and as a matter of best practice it undertook to ensure that prescribing information was printed on all such items in future.

### PANEL RULING

The Panel noted that the advertisement was stuck to the front cover of MIMS only down one side. The advertisement had formed a flap on the cover of MIMS and on the reverse had "Post-it Note" printed in faint type. It was detachable and could easily be removed and replaced or stuck elsewhere. The Panel's view was that given its format the advertisement had to be considered as a loose insert. It was not bound in or permanently fixed in some other way. The Panel noted Clause 5.2 of the Code that a loose insert in a professional publication could not be an abbreviated advertisement. The Panel considered therefore that the advertisement could not be an abbreviated advertisement. The prescribing information as required by Clause 4.1 of the Code should have been included. The Panel therefore ruled a breach of Clause 4.1 of the Code.

**Complaint received** **18 May 1998**

**Case completed** **29 June 1998**

CASE AUTH/712/5/98

# HOECHST MARION ROUSSEL NURSE ADVISOR v HOECHST MARION ROUSSEL

## Conduct of a representative

**A nurse complained about the conduct of a Hoechst Marion Roussel representative. The complainant had been employed by an agency to run a blood pressure clinic at a practice on behalf of the company. She had met the representative at the surgery for a briefing session and two situations had arisen which the complainant considered might breach the Code. Firstly the representative had asked to sit in on the clinic and had been surprised when the complainant refused. Secondly, the representative, when running through guidelines that another nurse had written, had said "some people would add in a diuretic if blood pressure was not well controlled" implying that she could add in another medicine if she wanted to. She noted that Hoechst Marion Roussel produced a diuretic. The complainant had been uncomfortable about the situation she found herself in and had left without undertaking the clinic.**

**The Panel considered that Hoechst Marion Roussel was responsible for the lack of preparation of the nurse. It noted that the company had since terminated its agreement with the agency in question. The nurse had been supposed to act as a nurse advisor to carry out a post switch review of patients changed to Tritace. As a consequence of the lack of preparation the nurse had left the clinic which had inconvenienced both the practice and patients. High standards had not been maintained and a breach of the Code was ruled. The Panel considered that the representative had been placed in a difficult position. He had attempted to give the nurse the information necessary for her to undertake the clinic and this had caused further problems. Although the representative had verbally reassured the complainant that he had not intended to criticise her nursing skills the opposite impression had been given. Contrary to instructions the representative had not maintained a high standard of ethical conduct and a further breach of the Code was ruled.**

A registered general nurse complained about the conduct of a senior medical representative of Hoechst Marion Roussel Ltd. The complainant had signed a contract with an agency as an independent nurse advisor. The agency placed nurses in general practices to run specific clinics on behalf of pharmaceutical companies.

### COMPLAINT

The complainant stated that on 14 May 1998 she had an assignment to run a blood pressure clinic at a practice. The complainant duly met the representative from Hoechst Marion Roussel at the surgery for a briefing session before the clinic was due to begin. During this time two situations arose which the complainant considered might breach the Code.

- The representative requested that he sat in on the clinic and was rather amazed when the complainant refused. He gave three reasons why he should do this; firstly, he wanted to know how "his patients" were doing. Secondly, he had "had problems" with other nurses before and considered that they did not know what they were doing (the complainant considered that this implied that she was incompetent). Thirdly, he said that another nurse well known to the agency had always let him sit in on sessions.
- The representative proceeded to tell the complainant about the clinic and was running through some guidelines that another nurse from the agency had written and, to the complainant's horror, said that she could increase patients' treatment if their blood pressure was not well controlled. The representative then went on to suggest that the complainant used the practice computer system to update their prescription issues. He then went on to say "some people would add in a diuretic if blood pressure was not well controlled". The complainant considered that the representative was implying she could add in another drug if she wanted to. The complainant stated that it was interesting to note that Hoechst Marion Roussel also produced a diuretic.

The complainant considered that the representative's suggestions were encouraging her to break the law.

The complainant stated that by this time she felt extremely uncomfortable about the situation she had found herself in and duly left the building, without undertaking the clinic.

The complainant stated that she was concerned that pharmaceutical company representatives should behave in such a manner. She was also concerned that agencies were "allowed" to supply nurses to the pharmaceutical industry in such a way. It appeared as if there was a loophole in the legislation that allowed nurses to be used by pharmaceutical companies in such a way.

### RESPONSE

Hoechst Marion Roussel first placed the issue in the context of its promotional strategy for Tritace (ramipril), an ACE inhibitor for the treatment of mild to moderate hypertension. Following the publication of the NHSE's Executive letter (95) 8 Annex B, which asked general practitioners to consider switching to therapeutically equivalent drugs wherever clinically appropriate, the company recognised the potential for general practitioners to make cost-savings in relation to their prescribing of ACE inhibitors. Hoechst Marion Roussel stated that Tritace was competitively priced in relation to others in the class and the company's basic proposition to a number of surgeries had been that by switching appropriate patients to ramipril from alternative ACE inhibitors, savings on the practice's medicine bill might be made without compromising high standards of patient care, thus freeing funds which might be utilised to the benefit of patients. The company was convinced that this was an entirely ethical and rational approach.

Hoechst Marion Roussel stated that it recognised that for

any individual practice a considerable workload and commitment was required to achieve a 'therapeutic substitution' as outlined above, if it was to be well managed from a practical point of view. The company had, therefore, appointed an experienced team of representatives, known as Healthcare Development Managers (HDMs), whose role it was to firstly discuss with practices the concept of therapeutic substitution and, if those practices decided to undertake such a process in connection with ramipril, to facilitate its initiation, monitoring and review.

Hoechst Marion Roussel stated that clearly it would be inappropriate for its representatives to have any clinical involvement in any of this process or to have access to any patient-specific information. The HDMs were therefore empowered, if so requested by the doctors involved, to brief an agency, retained by the company to supply appropriately trained and qualified independent personnel, to provide either a nurse adviser or IT specialist to attend the surgery in question to undertake parts of the switch process as directed by the doctors concerned. Hoechst Marion Roussel provided documentation which specified the qualifications and role and responsibilities of the nurse advisers (the role undertaken by the complainant), the agreement the company had in place with the agency and the document supplied to its HDMs clearly describing the role of all parties involved in the process of 'switch'. In addition a copy of the job specification sheet sent by the representative to the agency to arrange a series of clinics, including the one attended by the complainant were provided. The job specification sheet had been signed by a doctor at the practice, and clarified the fact that these clinics, and the representative's involvement with them, were occurring with the full knowledge and consent of the practice concerned.

Hoechst Marion Roussel stated that the representative in question was very experienced having been employed by the company for several years. He initially joined the company in August 1994 as a Hospital Representative and was subsequently promoted in January 1996 to the position of Healthcare Development Manager. HDMs were considered to have senior positions amongst Hoechst Marion Roussel's Primary Care sales teams and required a high level of technical and commercial expertise. The representative had passed the ABPI representatives examination in November 1989.

Hoechst Marion Roussel stated that it read the complainant's letter with grave concern and not a little surprise. Whilst the company recognised that, in what would appear to be the word of one person against another, there was room for some misunderstanding and misinterpretation. Hoechst Marion Roussel would nevertheless like to clarify the points raised by the complainant as seen from the representative's viewpoint. A statement made by the representative and provided to the agency was provided.

Hoechst Marion Roussel stated that the representative had assured the company that he was in no way intending by his comments or conduct, to imply that the complainant was in any way incompetent or to disparage her nursing skills (Clause 8.2) and indeed the company understood that he verbally reassured her to this effect. His actions in volunteering information to her were in response to the fact she appeared to be unaware of the nature of the particular clinic for which she was to be responsible (a review clinic for patients who had been switched from another ACE inhibitor to ramipril) and the overall aim of the project in hand. The representative did not intend to convey the impression that he was instructing her to change patients' medication or in any way act outside her role as nurse adviser as laid out in the nurse adviser role and responsibilities document. However, since the complainant did not seem to be familiar with the dosages of ramipril in clinical use it appeared to the representative to be important that she was made aware what they were and the range within which they might be adjusted.

Hoechst Marion Roussel acknowledged that the representative showed the complainant notes made by the previous agency nurse attending the practice and it might have been inappropriate to offer to 'sit in' on the clinic, but this was done in a spirit of wishing to be helpful in the instance where the complainant appeared to be experiencing a high degree of uncertainty as to her remit. Further, the company understood from the representative that the complainant had specifically requested information as to what had taken place in previous clinics. Hoechst Marion Roussel noted that the representative accepted the complainant's legitimate refusal to allow his presence during the clinic.

Hoechst Marion Roussel considered that there was clear evidence from the complainant's comments and those of the representative that the complainant had been inadequately briefed prior to her assignment for which the company held the agency responsible. The company noted that the agency were to ensure all nurse advisers were fully conversant with Tritace (ramipril) and with their role in the 'switch' process prior to attending at any surgery where their presence was requested. The role of the HDM was to brief the nurse as to the specific clinic she would be undertaking at a given practice and to introduce her to the relevant practice personnel. The situation in question meant that the representative was placed in a very difficult position, having a nurse arrive to conduct a clinic for which she was clearly unprepared.

Hoechst Marion Roussel accepted that due to the complainant's apparent lack of confidence in the task she would be undertaking, the representative, in his enthusiasm to ensure that a scheduled clinic would take place, might have placed himself in a potentially compromising situation. The company remained firmly convinced, however, that there were mitigating circumstances in this case and that the representative's overriding purpose was to avoid inconvenience to the surgery in question and to the waiting patients and not in any way to flout his obligations under the Code. This incident indicated that there was a significant communication gap and it was clear that there was the potential for misunderstandings to occur. The company, therefore, intended to review and clarify its guidelines further and following the outcome of this case would ensure that all relevant personnel were so briefed as to avoid any potential for further occurrences of this kind.

Hoechst Marion Roussel absolutely refuted the complainant's suggestion that the representative was in

some way trying to covertly 'promote' its diuretic which was, in any case, a generic product for which the company had relinquished promotional responsibility. The representative was merely trying to generally inform the complainant as to what strategy the responsible doctor might choose to adopt for patients whose hypertension was not initially well controlled on their starting dose of ramipril. The purpose of the clinic was to review the progress of patients who, it should be emphasised, had already been switched to Tritace. There was no question of this clinic, in any sense, being viewed by the representative as an opportunity to generate new business.

Hoechst Marion Roussel viewed this episode as most unfortunate in its outcome since both the practice and the patients involved were seriously inconvenienced by the complainant's abrupt departure and the company admitted to being surprised that she felt unable to at least discuss the conduct of the clinic with the duty doctor; however the company could only suggest this was a matter which the Authority might wish to discuss with her.

Hoechst Marion Roussel stated that due to a number of issues which had arisen in which the company felt that the service provided by the agency was not of adequate standard, the company had terminated its contract and had appointed a new agency. The company had prepared an information pack to brief both the new agency, its employees and Hoechst Marion Roussel's own staff regarding the 'switch' process which would be provided to the Authority on request.

Whilst Hoechst Marion Roussel considered that this whole episode was most unfortunate as discussed above, the company hoped that the Panel would accept its assurances that this was due to a series of misunderstandings and there was no intention on the part either of the company or its representative to breach any part of the Code.

**PANEL RULING**

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

In this particular case the Panel noted, as set out below, that the nurse was to carry out a "post-switch" review of patients. There had been no specific complaint as to whether this activity was acceptable under the Code and the Panel was therefore not required to make a ruling on it. The Panel queried, however, whether the stated objective in other instances, which was to assess the switching of patients for therapeutic substitution from current ACE inhibitor therapy to Tritace (Hoechst Marion Roussel's product) and the "post-switch" audit were legitimate activities. It seemed to the Panel that there was little difference in principle from the situation in a recent case (Case AUTH/689/3/98) in which a company had been ruled in breach of Clause 18.1 of the Code for providing finance to a health authority so that the health authority could reimburse costs incurred by practices when considering switching patients from a competitor's product to that of the donor company. The Panel decided that this should be taken up with Hoechst Marion Roussel under the provisions of Paragraph 16 of the Constitution and Procedure.

The Panel noted that the service agreement between Hoechst Marion Roussel and the agency was for the provision of "nurse advisors to undertake hypertension screening clinics to assess the suitability of patients for therapeutic substitution from current [ACE inhibitor] therapy to Tritace (ramipril) therapy". The complainant, however, had been engaged to perform a "post-switch" review of patients. The Panel noted that the service agreement stated that the nurse advisors would receive product training about Titrace both from the agency and from Hoechst Marion Roussel. The Panel noted that the complainant had arrived at the surgery having had no specific product training. In a letter written by the complainant to the agency, and supplied to the Authority, the complainant stated that she had been told that she was to run a blood pressure clinic but only found out from the representative that it was a post switch clinic when she arrived at the surgery. The complainant stated that that being so, she would have liked to have had the opportunity to read about Tritace before the visit. The complainant further stated that the agency had not told her the name of the medicine before the surgery visit and therefore she was unable to make an informed decision about whether to accept the assignment or not.

The Panel was concerned about the arrangements between the agency and Hoechst Marion Roussel for which, under the Code, Hoechst Marion Roussel was responsible. The Panel considered that this case was difficult. It had to make a decision on what had happened at the practice on the day in question. The acceptability or otherwise of the arrangements in principle was a matter that would be dealt with under Paragraph 16 of the Constitution and Procedure.

The Panel considered that the nurse had arrived to run a clinic for which she was totally unprepared and as a consequence of the lack of preparation the nurse had left the clinic. This had inconvenienced both the practice and the waiting patients. The lack of preparation was the responsibility of Hoechst Marion Roussel. The Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1 of the Code. The Panel noted that Hoechst Marion Roussel had since terminated its agreement with the agency.

The Panel noted that the representative's briefing document stated that "... it is imperative that HDMs do not get involved in any activity where they are given or seen to have access to information that contains both the name and address of patients". In addition the representative was told that "HDMs need only brief the [nurse advisor] regarding the job that they are booked for. [Agency] nurse advisors all have undertaken exams

during their initial training. If HDMs feel that there is any reason for concern then they need to contact [Hoechst Marion Roussel] IMMEDIATELY".

The Panel considered that the events had placed the representative in a difficult position. The representative had attempted to give the nurse the information necessary for her to undertake the clinic and this had caused further problems. The complainant had considered that the representative had criticised other nurses and implied that she was incompetent. The Panel noted that, although the representative had verbally reassured the complainant that he had not intended to disparage her nursing skills, the opposite impression had been given. The Panel noted that, contrary to instructions, the representative had requested direct access to patients by sitting in on the clinic. The Panel considered that the representative had not maintained a high standard of ethical conduct. A breach of Clause 15.2 was ruled.

**Complaint received** **20 May 1998**

**Case completed** **31 July 1998**

---

**CASE AUTH/713/5/98**

# WHITEHALL v SEARLE

## Powergel advertisement

**Whitehall Laboratories complained about a journal advertisement for Powergel (ketoprofen) issued by Searle. The advertisement detailed a review of trial data and was headed "How well do they work? Topical NSAIDs" with the subheading "Powerful new review demonstrates efficacy". Whitehall marketed Traxam (felbinac).**

**Whitehall alleged that differences which did not reach statistical significance had been presented in such a way as to mislead. The authors of the review categorically stated that "There is no clear message as to which of ketoprofen, felbinac, ibuprofen or piroxicam was best or indeed whether there was any difference in efficacy. They all worked". The advertisement, however, stated that ".... this review compares various NSAID gels and found that ketoprofen which is available as Powergel, was the most effective topical NSAID in terms of successful outcomes.**

**The Panel did not consider that the claims were adequately supported by the data. The differences between products did not achieve statistical significance. Further the claims were misleading as they did not reflect the stated views of the authors concerned. A breach of the Code was ruled.**

Whitehall Laboratories Ltd complained about an advertisement for Powergel (ketoprofen) issued by Searle which had appeared in Pulse in March and April 1998. The advertisement, which detailed a review of trial data (Moore *et al* (1998)), was headed "How well do they work? Topical NSAIDs" with the subheading "Powerful new review demonstrates efficacy". Whitehall marketed Traxam (felbinac).

### COMPLAINT

Whitehall alleged that the advertisement was in breach of Clause 7.2 of the Code. The claims made were misleading physicians and differences which did not reach statistical significance had been presented in such a way as to mislead.

Whitehall stated that the reference used to substantiate the claims made for Powergel was the meta-analysis on topical non-steroidal anti-inflammatory drugs (NSAIDs) by Moore *et al* recently published in the British Medical Journal. However, this review, contrary to Searle's claim, did not show that ketoprofen was better than the other topical NSAIDs, namely felbinac, ibuprofen and piroxicam. The authors categorically stated that "There is no clear message as to which of ketoprofen, felbinac, ibuprofen, or piroxicam was best or indeed whether there was any difference in efficacy. They all worked.".

Whitehall had asked Searle to justify the statement in the advertisement that "... this review compares various NSAID gels and found that ketoprofen which is available as Powergel, was the most effective topical NSAID in terms of successful outcomes". This statement was again reiterated underneath the bar chart in the advertisement: "In terms of successful outcome, ketoprofen was the most effective topical NSAID".

Furthermore, Searle asked the question in the advertisement (immediately above the bar chart) "Is there a difference between topical NSAIDs?". The answer was clear from the way in which the bar chart was presented and in the text below it; there was a difference and ketoprofen was the best. However, this answer was totally at variance with the conclusions of the authors of the meta-analysis that "There is no clear message as to which of ketoprofen, felbinac, ibuprofen, or piroxicam was best or indeed whether there was any difference in efficacy. They all worked.".

Searle's response to Whitehall's complaint had not in any way justified the use of these claims. Searle agreed that there were no statistically significant differences noted in the meta-analysis between either the number needed to treat (NNT) or the successful outcome results for ketoprofen, felbinac, ibuprofen and piroxicam. Although Searle maintained that no statistically significant differences claims had been alluded to, Whitehall believed that the differences as detailed in the bar chart and the statements made in the advertisement had been presented in such a way as to mislead most doctors. As would be appreciated, most doctors would not read and analyse the full meta-analysis in detail and the misleading claims made by Searle would be taken at face value.

Whitehall's objection was that the selective wording in the advertisement did not match up with the conclusion of the meta-analysis and was therefore misleading doctors into believing that ketoprofen, which was available as Powergel, was better than the others, a statement which was not supported by the authors' conclusions.

## RESPONSE

Searle submitted that it had not simply stated that ketoprofen was the most effective topical NSAID, but had qualified that claim by saying specifically "in terms of successful outcomes". This was of particular importance, since in the paper emphasis was placed on the definition of a clinically relevant successful outcome with a hierarchy of measures being established to make that assessment. "Successful outcomes" therefore related to a major and not a minor determinant of clinical efficacy. From these efficacy data, and the placebo response rates, the NNT could be derived, and this was an increasingly well recognised way of ranking therapies with respect to their ability to provide a given effect.

It was clear from table 2 in the review that ketoprofen provided the lowest NNT value and was the most effective in this respect. A comparison of successful outcomes could be obtained across the agents (including placebo) as shown in the bar chart. This was done by standardising the response rate for placebo and then for each treatment adding to the placebo response rate a value of 100 divided by the NNT for the treatment in question. A full explanation of how each value in the bar chart was calculated was provided.

The successful outcomes were ranked as shown in the bar chart, utilising the figures shown in table 2 of the review. In the same way as ketoprofen was the most effective topical NSAID as assessed by NNT, it was also the most effective in terms of successful outcome. The chart was a numerical one and statistical claims were not made.

In presenting the data in its advertisement, Searle had sought the opinion of one of the authors of the review to ensure that it was reflecting the evidence clearly and not misleading doctors.

Searle believed that the claims in question in the Powergel advertisement were supported by the meta-analysis in the review. The claims were accurate, reflected the evidence in the paper and were not misleading.

## PANEL RULING

The Panel noted that the meta-analysis featured in the advertisement (Moore et al (1998)) was undertaken to examine the evidence that topical NSAIDs were effective beyond their use as rubefacients and to determine whether there was any evidence for differences between the various products available. The authors analysed the results of 86 trials involving 10,160 patients, and pooled data for individual medicines which had been studied in at least three randomised trials. In acute conditions it was shown that ketoprofen, felbinac, ibuprofen and piroxicam were significantly superior to placebo. The authors stated, however, that there was no clear message as to which of them "... was best or indeed whether there was any difference in efficacy. They all worked.".

Conversely, the Panel noted that the advertisement, which was based on the paper, claimed that "In terms of successful outcome, ketoprofen was the most effective topical NSAID". The bar chart supporting the claim was headed "Is there any difference between topical NSAIDs?" and showed successful outcomes in terms of percentages of patients, these being ketoprofen 76.1%, felbinac 70.9%, ibuprofen 66.2%, piroxicam 61.4%, benzydamine 52.5% and placebo 37.6%. Searle had stated that the figures were obtained by standardising the response rate for placebo and then, for each treatment, adding to the placebo response rate a value of 100 divided by the NNT. Searle provided a rationale for this procedure. The Panel noted that the ranking of the products in the bar chart in terms of successful outcomes was the same as in the paper in terms of numbers needed to treat.

The Panel did not consider that the claims were adequately supported by the data. The differences between individual products did not achieve statistical significance. Further, the claims were misleading as they did not reflect the stated views of the authors concerned. A breach of Clause 7.2 of the Code was ruled.

**Complaint received** **27 May 1998**

**Case completed** **7 July 1998**

CASES AUTH/714/5/98 AND AUTH/725/6/98

# CHUGAI PHARMA v AMGEN and ROCHE

## Neupogen Syringe detail aid

**Chugai Pharma made a number of allegations about a detail aid for Neupogen (filgrastim) Syringe issued by Amgen and Roche.**

**In relation to a claim that efficacy had been demonstrated in the range of 4-8.4mcg/kg/day, Chugai said that the recommended dose of filgrastim in established cytotoxic chemotherapy was clearly stated in the summary of product characteristics (SPC) as 0.5MU (5mcg)/kg/day. The SPC did not say that efficacy had been demonstrated in the range 4-8.4mcg/kg/day, only that those doses had been used in clinical trials. The Panel considered that it was misleading to only state in the detail aid that efficacy had been demonstrated in the range 4-8.4mcg/kg/day when the SPC and the prescribing information quoted a specific recommended dose of 5mcg/kg/day. The information about doses used in clinical trials was information additional to the recommended dose but not a replacement for it. A breach of the Code was ruled.**

**The claims "for patients <75kg 1xNeupogen 30MU" and "for patients >75kg 1xNeupogen 48MU" were alleged by Chugai to represent unlicensed doses. The recommended dose was 0.5MU (5mcg)/kg/day. A single 30MU syringe was therefore appropriate for a patient of 60kg. A patient of 75kg would require 37MU (370mcg)/day. The Panel considered that the claims in question were misleading. The doses had been calculated from the claim that efficacy had been demonstrated in the range 4-8.4mcg/kg/day and not from the recommended dose of 5mcg/kg/day given in the SPC. At the recommended dose the 30MU syringe would be suitable for a patient up to 60kg. A breach of the Code was ruled.**

**No breach was ruled in relation to an allegation that the claim "The majority of healthcare professionals prefer pre-filled syringes" was misleading, a hanging comparison and an exaggerated claim. The Panel considered that it did reflect the available evidence as to the acceptability of pre-filled syringes. It was not a hanging comparison as given the context the comparison would be taken by implication to be other presentations of injectable products in general, and Neupogen vials in particular.**

**A table showed, according to various patient weights (60kg, 65-70kg and 75-90kg), the amounts of filgrastim and lenograstim (Chugai's product Granocyte) required to achieve a dose of 5mcg/kg of each, together with the corresponding costs. Chugai alleged that the cost comparison was misleading as the recommended dose of lenograstim for autologous PBPC mobilisation after cytotoxic chemotherapy was clearly stated in the SPC as 150mcg (19.2MIU)/m² daily and not 5mcg/kg. The Panel noted that the SPC for lenograstim stated that the dose was 150 micrograms (19.2 MIU) per m² daily. The following sentence in the SPC explained that this dose was therapeutically equivalent to 5 micrograms per kg daily, as used in clinical studies. The Panel noted that the table expressed the doses of both lenograstim and filgrastim in terms of micrograms per kg. The Panel considered that this would be less confusing to the reader than using two dosage units ie mcg/kg for filgrastim and mcg/m² for lenograstim. According to the Granocyte SPC the recommended dose of lenograstim, 150 micrograms (19.2MIU) per m² daily, had been correctly expressed as 5mcg/kg. No breach of the Code was ruled.**

Chugai Pharma U.K. Ltd made a number of allegations about a Neupogen (filgrastim) detail aid (ref P593290/797) issued by Amgen Limited. A photocopy of the detail aid, provided by Chugai, included the page bearing the prescribing information in which Roche Products Limited was named as the product licence holder. On receiving an original copy of the detail aid from Amgen it was seen that the otherwise blank back page of the detail aid bore the names of both companies, Amgen and Roche, in logo type together with the address of each. As a principle under the Code this meant that both companies were responsible for the detail and the complaint was thus also referred to Roche. Roche said that it endorsed the response already submitted by Amgen.

The detail aid was headed "Neupogen Syringe Convenience at no extra cost" and promoted the benefits of Neupogen pre-filled syringes compared with other presentations of growth factors in general and the Neupogen vial in particular. The detail aid briefly discussed dosing issues of Neupogen in neutropenic patients and compared the use of Neupogen and lenograstim for peripheral blood progenitor cell (PBPC) mobilization. Amgen stated that it had informed Chugai on 21 May 1998 that the detail aid had been withdrawn.

Chugai marketed Granocyte (lenograstim).

### 1 Claims "2 syringe sizes for convenient dosing in neutropenic patients*" and beneath this " *efficacy has been demonstrated in the range 4-8.4µg/kg/day"

#### COMPLAINT

Chugai said that the recommended dose of filgrastim in established cytotoxic chemotherapy was clearly stated in the summary of product characteristics (SPC) as 0.5MU (5mcg)/kg/day. The SPC for filgrastim did not state that efficacy had been demonstrated in the range 4-8.4mcg/kg/day, only that those doses had been used in randomised clinical trials. The suggestion that a dose either below or above 0.5MU (5mcg)/kg/day could be used was alleged to be in breach of Clause 3.2.

#### RESPONSE

Amgen said that it would address the second claim "efficacy has been demonstrated in the range 4-8.4µg/kg/day" since this was the focus of the Chugai complaint.

The sentence "efficacy has been demonstrated in the range 4-8.4µg/kg/day" was a statement of fact relating to the clinical trial data which were submitted to the Medicines Control Agency as part of the marketing authorization application. These data were published, Crawford *et al* (1991) and Trillet-Lenoir *et al* (1993).

The Neupogen SPC stated clearly that in randomised clinical trials this dosage range had been used. This statement was juxtaposed in the SPC with the recommended dose of 0.5MU (5mcg)/kg/day. The inclusion of this information within the SPC recognised that efficacy had been demonstrated at doses equal to or above 0.4MU (4mcg)/kg/day in the post-chemotherapy setting.

Amgen chose a 'recommended' dose of 0.5MU (5mcg)/kg/day as this was at the lower end of the effective range (but not the minimum effective dose). This was approved and the licensing authority also approved the wording with regard to the range used in randomised clinical trials.

The statement "efficacy has been demonstrated in the range 4-8.4µg/kg/day" was not a recommendation for use, but provided further information which might be relevant to prescribers. In addition, the recommended doses for the indications for which Neupogen had a marketing authorization were listed clearly in the prescribing information on page 5 of the detail aid.

The statement was not inaccurate, as Neupogen had been shown to be effective in the dose range 4-8.4mcg/kg/day. The approved wording of the Neupogen SPC clearly stated the dose range used in clinical trials. Therefore, the detail piece was not inconsistent with the SPC. Accordingly the claim "efficacy has been demonstrated in the range 4-8.4µg/kg/day" was not in breach of Clause 3.2 of the Code.

### PANEL RULING

The Panel noted that, with regard to the use of Neupogen in established cytotoxic chemotherapy, both the SPC and the prescribing information stated that the recommended dose was 5mcg/kg/day. The SPC gave further information regarding the route of administration of this dose before stating that in randomised clinical trials, a subcutaneous dose of 4-8.4mcg/kg/day was used.

The Panel noted that the detail aid contained the claim "2 syringe sizes for convenient dosing in neutropenic patients*". The asterisk referred to the statement "efficacy has been demonstrated in the range of 4-8.4µ/kg/day." The detail aid did not state that the recommended dose of Neupogen was 5mcg/kg/day.

The Panel considered that it was misleading to only state in the detail aid that efficacy had been demonstrated in the range of 4-8.4mcg/kg/day when the SPC and the prescribing information quoted a specific recommended dose of 5mcg/kg/day. In the Panel's view the information about the doses of Neupogen used in clinical trials was additional information to the statement regarding the recommended dose of Neupogen but was not a replacement for it. The claim referring to the use of 4-8.4µg/kg/day was not a fair reflection of the information given in the SPC regarding the recommended dose of Neupogen. The Panel considered that in the circumstances Clause 7.2 was the more appropriate clause. The Panel therefore ruled a breach of Clause 7.2.

## 2 Claims "for patients <75kg 1xNeupogen 30MU" and "for patients >75kg 1xNeupogen 48MU"

### COMPLAINT

Chugai said that the recommended dose of filgrastim for established cytotoxic chemotherapy was 0.5MU (5mcg)/kg/day. A single 30MU filgrastim syringe was therefore appropriate for a patient of 60kg. A patient of 75kg would require 37MU (370mcg)/day. It followed, therefore, that a single 48MU filgrastim syringe was appropriate for a patient of 96kg. Patients between the weights of 76 and 95kg would clearly receive a greater dose than recommended. Furthermore a single 48MU syringe was not appropriate for patients weighing more than 96kg. Chugai alleged that recommendation of unlicensed doses was clearly a breach of Clause 3.2 of the Code.

### RESPONSE

Amgen said that it supplied 2 vial/syringe sizes (30MU and 48MU) in order for healthcare professionals to administer Neupogen to patients of a wide range of body weights, avoiding the need for multiple injections.

Healthcare professionals often sought to use Neupogen, and similar products, in the most cost-effective manner. This could lead to actions which could not be supported by Amgen. Two such actions were:

- using doses below those shown to be effective in randomised clinical studies
- 'unit splitting' of single-use vials or syringes.

As discussed in response to 1 above, and as stated in the Neupogen SPC, in randomised clinical trials 4-8.4mcg/kg/day had been used. This dose range was applicable to patients of all weights treated with Neupogen following cytotoxic chemotherapy. Thus a 30MU Neupogen syringe would provide at least the minimum dose (demonstrated to be effective in randomized clinical trials) in patients up to a maximum body weight of 75kg. Similarly patients of up to 120kg would receive a dose demonstrated to be effective if treated with a Neupogen 48MU syringe (in the situation where the physician decided to dose at 4mcg/kg/day).

In the context of good clinical practice, the claim "for patients >75kg 1xNeupogen 48MU" could not reasonably be interpreted as a mandate or recommendation to use an entire syringe for patients greater than 75kg.

Neupogen Syringes were for single use only. An individual syringe had to be used for each patient, regardless of the amount of Neupogen required by that patient.

The Neupogen SPC stated "Neupogen contains no preservative. In view of the possible risk of microbial contamination, Neupogen vials and syringes are for single use only. Remaining solution should be discarded after dose withdrawal".

There was no implication that patients who were given the recommended dose of 5mcg/kg/day from a Neupogen 48MU syringe should receive more than this dose. Any additional Neupogen remaining in the syringe would be dealt with in accordance with the SPC and accepted clinical practice.

The claim "for patients >75kg 1xNeupogen 48MU" highlighted the cut-off point at which clinicians must change to the larger syringe to avoid the under dosing which would occur if a Neupogen 30 syringe was selected for the patient. This was important information as independent market research demonstrated that 26% of cancer patients weighed 75kg or more (source: ISIS, Cancer in Europe Study, 1997, UK Sample).

Moreover, Amgen had taken into account the United States' American Association of Clinical Oncology (ASCO) Guidelines. In the absence of comprehensive UK and EU recommendations on the prescribing of granulocyte colony stimulating factors, clinicians often resorted to the ASCO guidelines. These stated "that lower doses may be efficacious for CSF administration following chemotherapy and, as a consequence, rounding doses to the nearest vial size appears to be an acceptable clinical approach, with the potential to enhance convenience, reduce cost, and prevent wastage". Amgen had sought to clarify the minimum dose (4mcg/kg/day) which had been demonstrated to be effective in randomised clinical trials.

Amgen submitted that the claims were not inaccurate. Neupogen had been shown to be effective in the dose range 4-8.4mcg/kg/day, as appeared in the SPC. Therefore, a 30MU Neupogen syringe would provide an effective dose in patients up to a maximum body weight of 75kg. Similarly the claim "for patients >75kg 1xNeupogen 48MU" was designed to provide essential information of value to prescribers which was not inconsistent with the Neupogen SPC. Accordingly the claims were not in breach of Clause 3.2.

**PANEL RULING**

The Panel noted that the two claims referred to prefilled syringes of Neupogen containing either 30MU or 48MU. The claims appeared immediately beneath the statement referring to the use of Neupogen in doses of 4-8.4mcg/kg/day. The relationship between the strength of a Neupogen syringe expressed in MUs and a dose quoted in mcg/kg/day was not explained. The Panel noted, from the prescribing information that 30MU was 300mcg.

The Panel considered that the claims in question were misleading. The doses had been calculated from the claim that efficacy had been demonstrated in the range 4-8.4mcg/kg/day and not from the recommended dose of 5mcg/kg/day given in the SPC. At the recommended dose the 30MU syringe would be suitable for patients upto 60kg. The next size of the syringe would have to be used for patients heavier than 60kg. The Panel considered that in the circumstances Clause 7.2 was the more appropriate clause and a breach of that Clause was ruled.

**3 Claim "The majority of healthcare professionals prefer pre-filled syringes"**

**COMPLAINT**

Chugai stated that this claim was referenced to "Data on File. Amgen". These data referred to a telephone study conducted by a market research company on behalf of Amgen. The sample consisted of 10 hospital pharmacists, 20 physicians and 20 nurses. Such a small sample size could not possibly claim to represent the opinions of the majority of healthcare professionals. The claim was therefore misleading and in breach of Clause 7.2. The claim was also a hanging comparison (the majority of healthcare professionals prefer pre-filled syringes to what?) and an exaggerated claim. Breaches of Clause 7.2 and 7.8 were alleged.

**RESPONSE**

Amgen submitted that the aim of the study had been to demonstrate and confirm to the company the attitude of sampled practitioners to the benefits of the Neupogen syringe, and to validate the general consensus of literature that a syringe format was preferred over and above a vial. In a representative sample of key healthcare professionals, the study had demonstrated a strong preference for the Neupogen syringe over vials. Furthermore, an extensive literature search (abstracts and papers were provided) had unanimously concluded that pre-filled syringes had advantages when compared with vials or ampoule preparations.

The use of Neupogen was restricted to a clearly defined group of hospital physicians, supported by hospital pharmacists and specialist nurses. The definition of 'majority' in the context of the statement should be interpreted as 'the greater number'. The study demonstrated that more respondents expressed a preference for pre-filled syringes compared to vials.

The statement "the majority of healthcare professionals prefer pre-filled syringes" should be taken in the context of the page and the piece as a whole. The Neupogen syringe was being compared with other presentations of growth factors in general and the Neupogen vial in particular. The statement "Same price as the Neupogen vial" appeared at the foot of the page to clarify the comparison being made in the headline.

Amgen said that, with hindsight, the scope of the research could have been better explained and other evidence supporting the preference for pre-filled syringes included.

**PANEL RULING**

The Panel considered that the study gave some support to the claim "The majority of health professionals prefer prefilled syringes. The Panel noted that Amgen had provided additional references to support the claim. These references concurred with the results of the study. The Panel considered that the claim, based as it was on the small sample size of the study, nonetheless reflected the available evidence as to the acceptability to health professionals of pre-filled syringes. No breach of Clause 7.2 was ruled. The claim was not an exaggerated claim and no breach of Clause 7.8 was ruled.

The Panel noted that the claim "The majority of health professionals prefer prefilled syringes" appeared beneath the heading "Convenience at no extra cost" which was linked to the footnote "Same price as the Neupogen vial". The Panel considered that given the context the comparator, by implication, would be taken to be other

presentations of injectable products in general and Neupogen vials in particular. The Panel considered that given the context the claim was not a hanging comparison and ruled no breach of Clause 7.2 of the Code.

### 4 "Mobilisation with G-CSF and chemotherapy" (table)

A table showed, according to various patient weights (60kg, 65-70kg and 75-90kg) the amounts of filgrastim and lenograstim required to achieve a dose of 5mcg/kg of each, together with the corresponding costs.

#### COMPLAINT

Chugai stated that the recommended dose of lenograstim for autologous PBPC mobilization after cytotoxic chemotherapy was clearly stated in the lenograstim SPC as 150 micrograms (19.2MIU)/$m^2$ daily and not 5mcg/kg. The price comparison was therefore misleading as a price comparison should be made on the basis of the equivalent dosage requirement for the same indications. Chugai alleged a breach of Clause 7.2 of the Code.

#### RESPONSE

Amgen stated that the SPC for lenograstim clearly stated "This recommended dose of 150µg/$m^2$ daily is therapeutically equivalent to 5µg/kg daily, as used in clinical studies". Amgen had therefore reasonably relied upon Chugai's own SPC in making this statement.

Use of the mcg/kg dose allowed physicians, pharmacists and nurses to compare the two products on the same basis. The relationship between a dose quoted as mcg/kg with one quoted as mcg/$m^2$ might not be clear to the reader. The lenograstim SPC provided the conversion between the two methods of dosing lenograstim. 5mcg/kg daily was an equivalent dose for mobilization with chemotherapy for both lenograstim and Neupogen. Thus the price comparison was fair, balanced and valid.

It was important to point out that the situation in which lenograstim was less expensive than Neupogen had been given equal prominence in the detail aid to those where the cost was favourable to Neupogen.

The comparison was accurate and fair, and because it was comparing like with like it did not mislead. Accordingly, the table did not breach Clause 7.2.

#### PANEL RULING

The Panel noted that the SPC for Granocyte (lenograstim) stated that for the mobilization of PBPC's after cytotoxic chemotherapy the dose was 150 micrograms (19.2 MIU) per $m^2$ daily. The following sentence explained that this dose was therapeutically equivalent to 5 micrograms per kg daily, as used in clinical studies.

The Panel noted that the table expressed the dose of both lenograstim and filgrastim in terms of micrograms per kg. The Panel considered that this would be less confusing to the reader than using two dosage units ie mcg/kg for filgrastim and mcg/$m^2$ for lenograstim. According to the Granocyte SPC the recommended dose of lenograstim, 150 micrograms (19.2MIU) per $m^2$ daily, had been correctly expressed as 5mcg/kg. No breach of Clause 7.2 was ruled.

**Complaint received** **27 May 1998**

**Case completed** **10 August 1998**

CASE AUTH/717/6/98

# GENERAL PRACTITIONER v LILLY

## Distaclor MR mailing

**A general practitioner complained about a GP mailing for Distaclor MR (cefaclor) issued by Eli Lilly. The mailing was headed "Avoid additional strain on prescribing budgets through unwanted effects such as diarrhoea" beneath which a comparison of the absorption of cefaclor, co-amoxiclav, ciprofloxacin, erythromycin and clarithromycin was given in tabular form. It was alleged that there was no evidence that prescribing cefaclor in general practice was an option that could be justified on grounds of cost.**

**The Panel considered that the impression given by the mailing was that Distaclor was good for prescribing budgets. The mailing suggested that this was related to absorption and hence the incidence of diarrhoea. The heading referred to additional strain on prescribing budgets through unwanted side effects such as diarrhoea. The Panel had some criticisms of the data provided by Lilly. The Panel decided that in linking prescribing costs to one issue the mailing was misleading and a breach of the Code was ruled.**

A general practitioner complained about a GP mailing for Distaclor MR (cefaclor) issued by Eli Lilly and Company Limited (ref DCR 781). The mailing consisted of an A4 sheet headed "Avoid additional strain on prescribing budgets through unwanted side effects such as diarrhoea" beneath which a comparison of the absorption of cefaclor, co-amoxiclav, ciprofloxacin, erythromycin and clarithromycin was given in a tabular form.

### COMPLAINT

The complainant alleged that Lilly appeared to be claiming that Distaclor MR should be chosen on the grounds of avoiding a strain on prescribing budgets.

The complainant alleged that the mailing was misleading and that there was absolutely no evidence that prescribing cefaclor in general practice was an option that could be justified on the grounds of cost. For most of the infections seen in general practice, either trimethoprim, amoxycillin or one of the other non-patented traditional antibiotics were the recommended option. Cefaclor was not only a second line drug for most general practice problems, but it was also extremely expensive.

This mailing was misleading because it did not mention the cheaper and better alternatives to cefaclor, and because it made the unjustified link between highly dubious data on percentage absorption and the overall cost of managing the patient's problem.

### RESPONSE

Lilly submitted that it could not agree with the opinion of the complainant. Many commonly encountered pathogens in the community were now resistant to the antibiotics cited by the complainant, which had caused medical practitioners to use the antibiotics mentioned in the advertisement more frequently as first line therapy.

With regard to the complainant's view that cefaclor was not only a second line drug for most general practice problems but was also extremely expensive, Lilly pointed out that except for erythromycin, Distaclor MR was cheaper than other antibiotics mentioned in the advertisement.

The company did not agree that there were cheaper and better alternatives to cefaclor. The link between absorption rates and side effects was not dubious. The company stood by the suggestions that increased side effects such as diarrhoea were likely to require treatment, thus placing additional strain on prescribing budgets.

A paper by Borriello (1988) emphasised the importance of antibiotics which reached the gut and caused diarrhoea. The author also stated that cefaclor did not predispose the gut to colonisation by *Clostridium difficile* in his hamster model. A paper by Lacey (1988) stated that cefaclor was highly absorbed and highly absorbed antibiotics were less likely to disturb normal flora in the lower bowel. A paper by Beringer *et al* (1998) demonstrated the cost of *Clostridium difficile* infections secondary to antibiotic therapy.

Lilly submitted that these publications substantiated that well absorbed antibiotics such as cefaclor had less propensity to cause expensive side effects. Medical practitioners were using antibiotics mentioned in the advertisement more frequently as first line therapy because of increasing resistance which was demonstrated by their growing usage. The company provided moving annual total (MAT) data to support its view.

The company submitted that the need to change from some of the more commonly prescribed cheaper antibiotics was elegantly discussed by Trigg and Davies (1994).

### PANEL RULING

The Panel noted that the MAT data for prescriptions dispensed for Distaclor, co-amoxiclav, clarithromycin and ciprofloxacin showed an increase from a combined total of approximately 4.5 million in April 1992 to approximately 7 million in April 1998. There was no information as to why this increase had occurred. In the Panel's view it could not be assumed that this was due to increased use as first line agents. The Panel noted that between December 1995 and April 1998 the number of prescriptions for co-amoxiclav had steadily fallen.

The Panel noted that Lilly did not agree that there were cheaper and better alternatives to Distaclor but did not provide any supporting data. Distaclor was less expensive than all of the antibiotics listed in the mailing except erythromycin but it was more expensive than other antibiotics listed in MIMS and those referred to by the complainant. No comparative efficacy data had been provided.

The Panel noted that a review article was cited in support

of the 91-94% absorption of cefaclor quoted in the mailing. The absorption figures for the other products listed in the mailing were also from review articles. No details were given of the original studies and it was therefore difficult to assess the validity of the figures.

With regard to the link between absorption and overall cost of managing the patient, Lilly had provided further review articles to support the view that an antibiotic which was highly absorbed, such as Distaclor, was less likely to cause disturbance of commensal gut flora and consequently could be predicted to result in less frequent diarrhoea. Data was also provided on costs associated with the occurrence of *Clostridium difficile*-associated diarrhoea in antibiotic-treated patients in the USA but no data was provided on the costs of treating other side effects.

The Panel noted that the Beringer paper stated that "analysis of actual costs incurred due to antibacterial adverse effects are necessary" as "drug acquisition cost is only a component of the total direct cost and is not at all reflective of indirect costs or effectiveness of treatment". This supported the view that there may be a link between absorption and overall cost, via the incidence of diarrhoea. There was, however, no data relating to all direct and indirect costs associated with treatment and with all side effects (not just diarrhoea) taking into account efficacy. Without such data it was not known whether any indirect costs which might be saved by a possible reduction in diarrhoea were of sufficient magnitude to compensate for a higher initial direct cost of treatment.

The Panel noted that the editorial by Trigg and Davies, which supported a change from amoxycillin to cefaclor in order to limit disruption of normal flora, only examined the use of antibiotics in the treatment of bronchitis.

The Panel considered that the impression given by the mailing was that Distaclor was good for prescribing budgets. The mailing could be seen to be suggesting that this was related to absorption and to the incidence of diarrhoea. The heading referred to additional strain through unwanted side effects such as diarrhoea. The Panel noted its criticisms of the data provided by Lilly. The Panel decided that in linking prescribing costs to one issue the mailing was misleading and ruled a breach of Clause 7.2 of the Code

**Complaint received** **5 June 1998**

**Case completed** **31 July 1998**

---

**CASE AUTH/718/6/98**

# ALLERGAN v PHARMACIA & UPJOHN

## Xalatan brochure

**Allergan complained about a Xalatan (latanoprost) brochure used by Pharmacia & Upjohn's representatives.**

**A bar chart headed "How effective is Xalatan as long term monotherapy?" was ruled in breach because the Panel considered that the use of a suppressed zero exaggerated the difference between baseline and after treatment in relation to the lowering of intraocular pressure (IOP). It was important to consider the immediate visual impression created by the bar chart. It was irrelevant that the IOP would not be zero.**

**A table headed "How well tolerated is Xalatan?" compared Xalatan with a number of other products in relation to systemic adverse events, ocular adverse events and known drug reaction potential. The Panel considered that the table was ambiguous and misleading. The adverse events differed in their clinical importance and there was only limited prevalence data. A breach of the Code was ruled. A further breach was ruled because the Xalatan SPC stated that there were no definitive interaction data available whereas the table showed that there was no known drug interaction potential.**

**The phrase "in combination therapy" beneath the heading "Efficacy" was considered by the Panel to give the impression that Xalatan was licensed to reduce elevated IOP as monotherapy or as combination therapy. In the Panel's view this was not so as no such statement appeared in the indication section of the SPC. The SPC stated that definitive clinical trials of combination use had not been carried out and reference was made to the available data. A breach was ruled because the Panel considered that the page in question was misleading as it was not a fair reflection of the information in the SPC.**

Allergan Ltd complained about a Xalatan (latanoprost) brochure (ref P3159/97) used by Pharmacia & Upjohn Limited's representatives when promoting the product to ophthalmologists.

### 1 Use of a suppressed zero

Page 5 included a bar chart headed "How effective is Xalatan as long term monotherapy?" The bar chart showed intraocular pressure at baseline (25.3mmHg), 12 months (17.3mmHg) and 24 months (17.6mmHg). The vertical axis started at 15mmHg and finished at 27mmHg.

#### COMPLAINT

Allergan accepted that the title made it clear that the purpose of the bar chart was to indicate "how effective" Xalatan was, but as the bar chart included suppressed zeros, this gave a visually misleading impression of the data by accentuating the intraocular pressure lowering effect of latanoprost. A breach of Clause 7.6 of the Code was alleged.

#### RESPONSE

Pharmacia & Upjohn referred to Clause 7.6 of the Code which stated that "Graphs and tables must be presented in such a way as to give a clear, fair, balanced view of the matters with which they deal, ....." The supplementary information stated that particular care should be taken with graphs and tables to ensure that they did not

mislead and one of the examples given was by the use of suppressed zeros. While it might be true that in certain cases suppressed zeros might distort a graph, this was clearly not true in all instances and could be left out for the sake of expediency where the "zero" point was irrelevant to the parameter measured.

This was definitely the case with intraocular pressure (IOP) where the normal IOP was never zero, but instead was within a range of 10-21mmHg with the average being 16mmHg. In this instance, then, the "zero point" on the graph was not 0mmHg. The target of antiglaucoma therapy was the reduction of elevated IOP to within the normal range. This was reflected in the published clinical papers and promotional material in which the "zero" ranged from 14 to 18mmHg. Indeed, the use of a zero in such a bar chart would in fact very much accentuate the change in IOP. Pharmacia & UpJohn provided a copy of the bar chart drawn with an interrupted vertical axis.

Pharmacia & Upjohn stated that in glaucoma, very small changes in IOP were extremely important in relation to disease progression. The average antiglaucoma agent reduced IOP by 20-30% which when used in a glaucoma patient with a typical IOP of 25mmHg would affect an IOP of 17.5-20mmHg. A change of 5-7.5mmHg would be poorly represented if a complete scale of 0-30 mmHg was utilised.

For these reasons the company submitted that the bar chart, in its current format, did not distort or misrepresent the facts. Furthermore, the addition of numerical values to the various bars in the chart made it virtually impossible to misread the data presented.

The issue with the bar chart then became whether or not it intended to mislead the target audience and whether or not the audience could be misled by the use of such a bar chart. The very nature of glaucoma disease meant that it was diagnosed, treated and monitored by ophthalmology specialists. Medical therapeutic options were initiated by such professionals with continuing supplies being provided by general practitioners. The target audience for Xalatan was, therefore, practising ophthalmologists who possessed an intimate knowledge of the disease area.

Given the fact that bar charts using this format were standard in the published literature and that the aim of therapy was the reduction of IOP to within the normal range, the company did not accept that the bar chart could possibly mislead practising ophthalmologists. Clearly there was no intention to mislead on the part of Pharmacia & Upjohn.

## PANEL RULING

The Panel considered that the use of the suppressed zero in the bar chart exaggerated the difference between baseline and after treatment. It was important to consider the immediate visual impression created by the bar chart. It was irrelevant that IOP would not be zero. The graph was misleading. The Panel therefore ruled a breach of Clause 7.6 of the Code. It did not consider that the bar chart provided by Pharmacia & Upjohn with an interrupted vertical axis would be acceptable.

### 2 Comparison of adverse events and known drug interaction potential

Page 7 featured a table headed "How well tolerated is Xalatan?" The table compared dorzolamide, brimonidine, timolol, pilocarpine and Xalatan with respect to three parameters, systemic adverse events, ocular adverse events and known drug interaction potential. Each medicine was "scored" against each parameter by the use of none, one, two or three red dots. The red dot was described beneath the table as "Relative data sheet weightings".

## COMPLAINT

Allergan alleged that the table was misleading. In Allergan's opinion it was not possible to compare side effects in this simplistic way as they differed widely in clinical importance, for example, body rash (dorzolamide summary of product characteristics (SPC)), heat block (timolol data sheet), fatigue/drowsiness (brimonidine SPC)). Grouping these as systemic adverse events and comparing prevalence from the weighting on the SPC or data sheet, where usually no numerical incidence was quoted, was misleading. The relative data sheet weightings were thus unsubstantiated, subjective and misleading.

The table also implied that latanoprost had no known drug interaction potential which was not reflected in Section 4.5 of the SPC which stated under interactions that "definitive drug interaction data are not available".

Breaches of Clauses 7.2, 7.3 and 7.7 of the Code were alleged.

## RESPONSE

Pharmacia & Upjohn stated that the medical treatment of primary open angle glaucoma was particularly prone to poor patient compliance. The reasons were well known and documented. These being:

1 asymptomatic disease

2 chronic disease leading to long term need for treatment

3 benefit of treatment not apparent

4 several medications, administered both ocularly and orally/systemically

5 local side effects

6 systemic side effects

All these factors need to be taken into consideration when prescribing a glaucoma medication in order to reduce the risk of non-compliance.

As data were not available to make a direct quantitative comparison of points 4, 5 and 6, above, the semi-quantitative/semi-qualitative schematic diagram used was decided upon as the most appropriate way of visually indicating which of these aspects of therapy required serious consideration/patient counselling before prescribing one of the five products mentioned. The table was prepared taking the relative data sheet/SPC weightings for each product into consideration, in other words, mention of "most common"/"most frequently reported"/entry in contra-indication/special warnings

and precautions/undesirable effects sections.

Sections of the relevant SPC/data sheets (ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1996-1997) referring to ocular and systemic adverse events and associated warning/precautions were provided. Pharmacia & Upjohn submitted that independent publications discussing the relevant merits of different ocular antiglaucoma medications mirrored the SPCs and the table. For example, as would be seen from the Xalatan SPC, systemic adverse events were rare and therefore it was deemed appropriate to use this as the product with the lowest risk of systemic effects, allocating the weightings for the other compounds in relation to this. Conversely, the ocular adverse events experienced by patients using Xalatan warranted the highest relative weighting and the relevance of this compared to other agents particularly timolol (the gold standard treatment) could be seen.

With regard to known drug interaction potential, the table reflected clearly what was included in the SPCs/data sheets for all five medicines. As open angle glaucoma patients tended to be more than 60 years old, the potential for drug interactions was particularly important because patients were usually taking concomitant medications. Concern over potential drug interactions associated with topical glaucoma medication and other systemic medications have been discussed in the literature.

The table was not created to be misleading, it was created purely to highlight which aspects of the patient's treatment need addressing to maximise compliance, and needed to be considered/discussed with the patient when prescribing each of the given medications. It must also be remembered that the booklet was used by medical representatives as an illustration aid when discussing Xalatan and various other antiglaucoma agents. They were therefore, able to put the table into context. As it was only used when speaking to practising ophthalmologists who were fully conversant with these agents, particularly the more established medications, then the table could not be seen to mislead.

Pharmacia & Upjohn submitted that drug interactions were not generally considered to be a problem with prostaglandins. Latanoprost was a prostaglandin $F_{2\alpha}$ analogue which after ocular instillation was approximately 88% absorbed, resulting in a plasma $C_{max}$ of 53pg/ml after 5 minutes. The half life was 17 minutes and given the once daily dosage, the chance of a drug interaction was, therefore, minimal. In light of this, definitive drug interaction studies had not been performed and were unlikely to be. Pharmacia & Upjohn referred to an SPC for a different prostaglandin $F_{2\alpha}$, Prostin $F_{2\alpha}$. This was given in high doses intra-amniotically for the termination of pregnancy. It had been available for a number of years and the drug interaction section mentioned only oxytocin.

The table clearly reflected that the relative need for concern over potential drug interactions was therefore minimal.

With regard to the alleged breach of Clause 7.7, Pharmacia & Upjohn submitted that the information supplied reflected available evidence and was substantiated by clinical experience and referred to comments by a named consultant ophthalmologist.

The table did not state that latanoprost had no side effects, instead it used latanoprost as the minimal starting point for drug interactions and systemic adverse events (as reflected by the absence of both of these from the SPC).

Finally, the use of this type of schematic diagram was not limited to Pharmacia & Upjohn, indeed it had been used in previous promotion by the complainant and by other companies Examples were provided.

### PANEL RULING

The Panel did not accept Pharmacia & Upjohn's submission that the medical representative would explain the table to ophthalmologists. Each piece of promotional material had to stand alone.

The Panel considered that the table was ambiguous and misleading. It was unacceptable to compare the products in this way as the adverse events differed in their clinical importance. There was only limited prevalence data for the products. The Panel ruled a breach of Clause 7.2 of the Code. The Panel noted that the SPC for Xalatan stated that there were no definitive drug interaction data available whereas the table showed that there was no known drug interaction potential. The Panel considered that this was not an accurate reflection of the SPC. The Panel therefore ruled a breach of Clause 7.2 of the Code. The Panel decided there was no need to make separate rulings concerning Clauses 7.3 and 7.7 as these were covered by its rulings of a breaches of Clause 7.2.

## 3 Alleged promotion of an unlicensed indication

Page 10 was headed "Why prescribe Xalatan?" beneath which appeared a visual implying that a balance had to be achieved between efficacy and patient tolerance. Beneath the word "Efficacy" the bullet points "As monotheraphy" and "In combination therapy" appeared. Beneath the words "Patient tolerance", the bullet points "Side effects" and "Compliance" appeared.

### COMPLAINT

Allergan alleged that the page suggested that latanoprost should be prescribed in combination therapy which appeared to promote usage outside the limits of the licensed indication. The indication for use in combination with other agents was removed from the latanoprost SPC in May 1997 following the European Mutual Recognition Procedure. Allergan provided copies of the old and new SPCs. A breach of Clause 3.2 of the Code was alleged.

### RESPONSE

Pharmacia & Upjohn failed to understand how the SPC changes arising from the Mutual Recognition Procedure had any relevance in this case. The reasons behind the changes to the SPC during Mutual Recognition reflected the need to reconcile national interpretations of the types of information to be included under the various sections. This was an inevitable consequence of the need to agree a single SPC for Europe as a conclusion to the procedure.

Pharmacia & Upjohn submitted that it was not appropriate to include any confidential details in support of this point, although it could assure the Panel that the company obtained agreement in all-party discussion with the Reference and Concerned Member States that mention of Xalatan in combination therapy was appropriate. In other words, the changes agreed to the original UK SPC were the result of accommodating national approaches to the presentation of prescribing information, rather than concern over the use of Xalatan in combination therapy.

To illustrate the point, the revised indication statement reflected the national traditions of some Member States to describe the medical condition concerned and virtually nothing else. However, Member States agreed that practical advice to the ophthalmologist on the use of Xalatan in combination was desirable and ethically necessary, given the polypharmacy nature of glaucoma management. Indeed the revised indication statement was carefully worded in a way which did not preclude combination treatment. The reference to patients who were "insufficiently responsive to another intraocular pressure lowering medication" emphasised the point. Further reference to the use of Xalatan with other topical ophthalmic medicines was found under Section 4.2, which gave the specific advice "If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart".

Furthermore, information on Xalatan in combination with other commonly used antiglaucoma agents was provided under Section 5.1 to enable the clinician to manage patients in the appropriate way, ie:

> "Pivotal studies have demonstrated that Xalatan is effective as a single drug therapy. Although definitive clinical trials of combination use have not been done, a three month study shows that latanoprost is effective in combination with beta-adrenergic antagonists (timolol). Short term (1 or 2 weeks) studies suggest that the effect of latanoprost is additive in combination with adrenergic agonists (dipivalyl epinephrine), oral carbonic anhydrase inhibitors (acetazolmide) and at least partly additive with cholinergic agonists (pilocarpine)".

In conclusion, Pharmacia & UpJohn stressed that the booklet was entirely consistent with the terms of the original and revised Xalatan SPC and totally refuted the complaint and the suggestion that the material was in breach of the Code .

## PANEL RULING

The Panel considered that the use of the phrase "In combination therapy" beneath the heading "Efficacy" gave the impression that Xalatan was licensed to reduce elevated IOP as monotherapy or as combination therapy. In the Panel's view this was not so as no such statement appeared in the indication section of the SPC. The Panel did not consider that the advice to administer topical opthalmic medicines at least five minutes apart supported the company's submission that the product could be used in combination therapy to lower IOP. The Panel noted that the SPC gave some advice about combination therapy in section 5.1. The SPC stated that definitive clinical trials of combination use had not been carried out and reference was made to the available data.

Overall the Panel considered that the page was misleading as it was not a fair reflection of the information given in the SPC. The Panel considered that in the circumstances Clause 7.2 was the more appropriate clause. The Panel therefore ruled a breach of Clause 7.2 of the Code.

**Complaint received** **11 June 1998**

**Case completed** **31 July 1998**

CASE AUTH/719/6/98

# SCHERING-PLOUGH v UCB PHARMA

## Promotion of Zirtek

**Schering-Plough complained about the tactics used by UCB Pharma in the promotion of Zirtek (cetirizine). A consultant otolaryngologist had been told by a UCB representative that Zirtek was the only WHO (World Health Organisation) approved antihistamine. Schering-Plough said that the WHO did not approve or certify medicines and had certainly not done so in respect of cetirizine. Similar verbal complaints from health professionals indicated that this misrepresentation was widespread and appeared to be a deliberate campaign.**

**The Panel noted that the basis of the statement was a letter in The Lancet from the WHO Collaborating Centre for International Drug Monitoring which had examined the cardiac and sudden death risk profiles for the five most commonly prescribed non-sedating antihistamines. Various data were presented in a bar chart. The text referred to the results for terfenadine, astemizole and loratadine. No comment was made in the text in relation to cetirizine or acrivastine although the data showed that both were associated with lower reporting rates than the other three. The Panel noted that there was a conflict of evidence as to what the representative had said. It was alleged that the representative had said that Zirtek was the only WHO approved antihistamine. The representative denied this but stated that she had said that cetirizine was the only non-sedating antihistamine not subject to a warning notice in the article. The Panel noted that this was inaccurate because there had been no warning about acrivastine either, and ruled a breach of the Code. A further breach was ruled in respect of the representatives' briefing material for Zirtek. The Panel did not consider that the lack of a warning in the WHO letter amounted to a positive endorsement as implied in the briefing material. The briefing material would mislead representatives on the matter and be likely to lead to a breach of the Code.**

Schering-Plough Ltd complained about the tactics used by UCB Pharma Limited in the promotion of Zirtek (cetirizine). The company submitted a letter which it had received from a consultant otolaryngologist about remarks made by a representative.

### COMPLAINT

The consultant had been told by the Zirtek representative that Zirtek was the only WHO (World Health Organisation) approved antihistamine. Schering-Plough stated that the WHO did not approve or certify medicinal products and certainly had not done so with respect to cetirizine. It was alleged that the statement regarding the WHO approval of Zirtek was false in breach of Clause 7.2 of the Code.

Schering-Plough added that similar verbal complaints received from health professionals indicated that this misrepresentation of Zirtek was widespread and appeared to be part of a deliberate campaign.

### RESPONSE

UCB Pharma stated that it was somewhat puzzled by a number of aspects of the complaint, not least the delay between the date of the alleged incident and when Schering-Plough saw fit to raise the matter. Although the representative concerned had since left UCB to work for another company, she had been able to provide details of the meeting referred to in Schering-Plough's complaint. The meeting had been organised by an ENT audit committee and UCB had agreed to a request to sponsor the event financially. A full list of the attendees (21 ENT consultants and a specialist nurse) was provided. UCB noted that its representative was fully aware of the fact that the meeting was attended by Schering-Plough representatives who also manned a stand.

UCB stated that whilst a speaker was setting up their presentation talk the UCB representative was asked by the consultant if she would give "a few words on her company's product". The representative categorically denied making a statement that "Zirtek was the only WHO approved antihistamine" as alleged by Schering-Plough. However, she did make reference to an article in The Lancet (Lindquist and Edwards (1997)) which originated from WHO entitled "Risks of non-sedating antihistamines" and did comment that cetirizine was the only non-sedating antihistamine not subject to a warning statement within the article. UCB believed that such a comment was perfectly reasonable and in line with UCB's briefings to its representatives. A copy of the representatives' briefing material was provided.

The representative had commented that following her talk she was thanked personally by the consultant and asked if she would speak at, and sponsor, future meetings of the ENT audit committee. UCB therefore found the consultant's letter surprising in these circumstances. Neither UCB nor the representative had any record of receiving a direct communication from the consultant expressing any concern at the representative's actions at the meeting. The representative had joined UCB in February 1997 and had left the company in January 1998. She had not previously been employed as a medical representative before joining the company and had not taken the Medical Representatives Examination.

### PANEL RULING

The Panel noted that The Lancet paper was a letter written from the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden. The authors, Lindquist and Edwards, examined the cardiac and sudden death risk profiles of the five most commonly prescribed non-sedating antihistamines, acrivastine, astemizole, cetirizine, loratadine and terfenadine. Spontaneous adverse drug reaction (ADR) report profiles 1986-96 were examined with the use of data from the WHO ADR database. Reporting rates for 1986-96 for cardiac rate and rhythm disorders, subset of these disorders, and death as a result of cardiac rate/rhythm reaction or reported as sudden death in relation to number of reports per million defined daily doses sold,

were presented in a bar chart. The text referred to the results for terfenadine, astemizole and loratadine. No comment was made at all about either cetirizine or acrivastine although the data showed that both were associated with lower reporting rates than those for terfenadine, astemizole and loratadine.

The letter was based on an analysis of spontaneous ADR reports and the Panel noted that such reports did not necessarily reflect the true incidence of an event. The authors stated that the crude reporting rates quoted in their letter reflected doctors' concerns about the non-sedating antihistamines but did not provide a definitive answer. A commentary in the same issue of The Lancet stated that although the reported rate of cardiac events and sudden death was low for all five medicines investigated, the Committee on Safety of Medicines needed to keep a close eye on all non-sedating antihistamines.

The Panel noted that there was a conflict of evidence as to what the representative had said. Schering-Plough alleged that the representative had said that Zirtek was the only WHO approved antihistamine. The representative denied this but stated that she had said that cetirizine was the only non-sedating antihistamine not subject to a warning statement within the article. The Panel noted that in addition to cetirizine, acrivastine was also not subject to a warning statement in the article. The representative's comments had thus been inaccurate.

The Panel examined the representatives' briefing material supplied by UCB Pharma which instructed the representative on how the product should be promoted. The briefing material was entitled "A Safety profile with Significantly Fewer Concerns than Other 2nd generation Antihistamines" with the sub-title "Recently acknowledged by WHO Lancet May 1997 and EAACI position paper 1996". The briefing material discussed the Lindquist and Edwards letter and stated that Zirtek's excellent safety profile had been acknowledged in the WHO paper. In an example of what a representative might say to a doctor the following was suggested: "Doctor, the WHO is currently confirming what we have been telling you for years: Zirtek is a safe drug". The Panel noted that the briefing material later stated that "It has to be stressed that the Lancet publication does not contain any warning against cetirizine ...". The Panel did not consider that the lack of warning in The Lancet letter amounted to positive endorsement of the product as implied by the briefing material. The briefing material ended with the statement "... choose Zirtek, because Zirtek is the safest". The Panel noted the comments made above about the use of spontaneous ADR reports. The Panel considered that the briefing material would mislead representatives with regard to the WHO's position on cetirizine (Zirtek) and was likely to lead to a breach of the Code. The Panel therefore ruled a breach of Clause 15.9. The Panel also noted that Zirtek had been described as "safe" and as "the safest" which was unacceptable in relation to Clause 7.7 of the Code which prohibited the use of the word "safe" without qualification. The Panel requested that this be drawn to the company's attention.

The Panel noted that the complaint had arisen from a meeting attended by the representative and the consultant who had subsequently written to Schering-Plough. In the Panel's view, what the representative had said had been influenced by her briefing material. The complainant had alleged a breach of Clause 7.2 but the Panel considered that as the complaint involved the activity of a representative Clause 15.2 was more appropriate and ruled a breach of that clause.

**Complaint received** **12 June 1998**

**Case completed** **10 August 1998**

CASE AUTH/720/6/98

# FORMER HEALTH SERVICE MANAGER v BOEHRINGER INGELHEIM

## Oramorph advertisement in Health Service Journal

**A former health service manager complained about an advertisement for Oramorph (morphine sulphate) issued by Boehringer Ingelheim which had appeared in the Health Service Journal, alleging that it was in breach because it was an advertisement for a prescription only medicine and because the content of the advertisement was not appropriate for the audience.**

**The Panel noted that the journal was a specialist title and was not aimed at the general public. The key factor was to whom a publication was aimed rather then whether it could be purchased by the general public. The Panel did not accept that the advertisement was an advertisement to the public as alleged. The journal was an acceptable vehicle for advertisements for prescription only medicines and no breach was ruled in that regard.**

**The Panel noted that the advertisement was headed "In your hands...." and referred to readers as palliative carers. It was aimed at clinicians and not at the journal's readership which was mainly administrative and general management personnel. A breach of the Code was ruled.**

A former health service manager complained about an advertisement which had appeared in the Health Service Journal on 11 June 1998. The advertisement was for Oramorph (morphine sulphate) and had been issued by Boehringer Ingelheim Limited (ref BIHD2181). The advertisement was headed "In your hands she has one thing less to fear about cancer". The text below detailed the use of oral morphine in the control of severe pain. The strapline at the bottom of the advertisement read "Working together to beat cancer pain".

### COMPLAINT

The complainant alleged that the advertisement was in breach of the Code because it was for a prescription only medicine which appeared in a journal for health managers. Further the content was not appropriate for the audience.

The Authority asked Boehringer Ingelheim to consider the provisions of Clauses 12.1 and 20.1 of the Code.

### RESPONSE

Boehringer Ingelheim stated that there appeared to be two issues raised by the complainant: that a prescription only medicine should not be advertised in the Health Service Journal and that the content of the advertisement was not appropriate to the journal readers.

Boehringer Ingelheim stated that these two issues were clearly linked and depended on the nature of the journal readers, their role in health care and their interest in therapeutics. It was noteworthy that in addition to the Oramorph advertisement, the inside cover of the June edition of the Health Service Journal contained an advertisement for a prescription only medicine. The publishers had provided Boehringer Ingelheim with details of the readership of the Health Service Journal. In Boehringer Ingelheim's view it was clear that the readership of the journal was intimately concerned with the NHS and its provision of health care to the community. Such readership could not be regarded in the same way as was described in Clause 20.1 of the Code for members of the general public but rather fell within the description in Clause 1.1 of the Code as to those to whom promotion of medicines must comply with the Code.

Boehringer Ingelheim then dealt with the question of whether or not the content of the advertisement was appropriate for the readers.

Boehringer Ingelheim stated that the Oramorph advertisement was identical to that promoting the product to hospital doctors and nurses. The purpose of carrying the same advertisement in the Health Service Journal was to ensure that its readership was informed on what was being said to doctors and nurses about the product. In this way it was expected that all would be familiar with the claims being made for Oramorph and have an opportunity for enquiries to the company if any reader would wish for further information. The company believed that the advertisement would encourage better understanding of Oramorph in different sectors of the NHS and was not expected to give rise directly to prescription or supply of the medicine.

Boehringer Ingelheim therefore submitted that the advertisement was entirely appropriate and did not breach either Clause 12.1 or 20.1 of the Code.

### PANEL RULING

The Panel noted that Clause 1.1 of the Code stated that the Code applied to the promotion of medicines to members of the UK health professions and to appropriate administrative staff. The relevant supplementary information referred to Clause 12.1 which required that promotional material should only be sent or distributed to those persons whose need for, or interest in it, could reasonably be assumed. The supplementary information to Clause 12.1 stated that promotional material should be tailored to the audience to whom it was directed.

The Panel noted that there had been a previous case concerning an advertisement for a prescription only medicine in a publication for healthcare workers (Case AUTH/145/4/94). The Panel had considered that the advertisement was not an advertisement to the public as alleged and that the publication was an acceptable vehicle for advertisements of prescription only medicines.

The Panel examined the materials now before it. The Health Service Journal was a specialist professional title and was not aimed at the general public. The Panel considered that the key factor was to whom the

publication was aimed rather than whether it could be purchased by the general public. The Panel did not accept that the advertisement was an advertisement to the public as alleged and considered that the publication was an acceptable vehicle for advertisements of prescription only medicines. The Panel therefore ruled no breach of Clause 20.1 of the Code.

The Panel then considered whether the content of the advertisement was suitable for the readership of the journal. The information from the readership survey showed that the journal was mainly read by administrative and general management personnel and by only a small number of clinicians. The publisher stated that the Health Service Journal was for the wide range of professionals who managed the provision of healthcare.

The Panel noted that the Oramorph advertisement was headed "In your hands..." and referred to readers as palliative carers. The Panel considered that the wording of the advertisement was such that it was aimed at clinicians. It had not been tailored to the audience. The Panel therefore ruled a breach of Clause 12.1 of the Code.

**Complaint received** **11 June 1998**

**Case completed** **15 July 1998**

---

**CASE AUTH/721/6/98**

# HOSPITAL PHARMACIST v SERVIER

## Highlights From ... The European Cardiologist Journal by Fax

**A hospital drug information pharmacist complained about a mailing entitled "Highlights From.... The European Cardiologist Journal by Fax" which he had received from Servier. His first impression was that the articles were taken from a well known journal called "The European Cardiologist Journal" but this did not appear to be the case. The publication appeared to be a promotional newsletter and it would seem that Servier had created a fictitious journal which was not available in any library. It was alleged that the mailing was disguised promotional material.**

**The Panel considered that the title gave the impression that it contained extracts from an independently produced journal. Some readers would assume that it was part of an abstracting, or similar, service. This impression was strengthened by the statement "Provided as a service to medicine by Servier Laboratories". The Panel noted that the papers were written by contributers at the invitation of Servier International but did not consider that this origin was adequately explained. Readers of the material might regard the papers differently if they knew how they had been generated. The Panel noted Servier's view that the mailing had clearly been presented as promotional material. The Panel did not consider, however, that the role of the company in the generation of the papers had been made sufficiently clear and a breach of the Code was ruled.**

A hospital drug information pharmacist complained about an A4, 8 page mailing (ref 98C0MA303) sent by Servier Laboratories Ltd. Servier, although not a member of the ABPI had agreed to comply with the Code.

The mailing was entitled "Highlights From ... The European Cardiologist Journal by Fax". The Servier logo and company name, together with the statement "Provided as a service to medicine by Servier Laboratories" were given on the front cover. The inside front cover consisted largely of a "Dear Colleague" letter from the Assistant Project Manager - Cardiovascular Products. The letter welcomed readers to the first edition of the "Highlights from the European Cardiologist-Journal by Fax" and explained that it was an international postgraduate training service. The eight annual editions of the mailing would contain a diverse selection of articles from the Journal by Fax all of which were totally independent and written by eminent European cardiologists. Beneath the letter was a list of contributing authors. There then followed five pages of short cardiology papers. The outside back cover carried an advertisement for Coversyl.

### COMPLAINT

The complainant stated that his first impression was that the articles appearing in the publication were taken from a well known journal called "The European Cardiologist Journal" of which articles contained therein were available by fax on request.

This did not appear to be the case. There was a well known periodical called "The European Journal of Cardiology" which was now called "The International Journal of Cardiology". The publication by Servier appeared to be some sórt of promotional newsletter which it had called "Highlights From... The European Cardiologist Journal by Fax". It would seem that the company had created some sort of "fictitious" journal which was not available in any library.

The complainant alleged that the mailing was in breach of Clause 10.1 of the Code in that it appeared to be disguised promotional material.

### RESPONSE

Servier explained that Servier International was responsible for a service known as "The European Cardiologist - Journal by Fax". Eminent European cardiologists were invited to write articles on subject which they considered of interest to their colleagues. These articles were sent by fax, under the author's name, to cardiologists who had requested to receive them, with a statement that "The European Cardiologist - Journal by Fax" was supported by an educational grant from Servier.

Servier stated that the mailing which was the subject of this complaint contained five articles selected from "The European Cardiologist - Journal by Fax". This piece was produced by Servier Laboratories, and sent as a mailing

on 8 June 1998 to senior hospital doctors in cardiology, diabetes, general medicine, geriatrics and clinical pharmacology; GPs with specialist interest in cardiology, hypertension and diabetes; hospital drug information and formulary pharmacists and health authority medical and pharmaceutical advisers.

Servier stated that "Highlights from The European Cardiologist - Journal by Fax" was clearly presented as promotional material. It was mailed second class and the envelope had the company's logo and address on the front and an address label with code number. The format and appearance of the piece was consistent with that of promotional material. The Servier logo and the statement "Provided as a service to medicine by Servier Laboratories" appeared prominently on the front page. Page 2 consisted of a welcome letter from the "Assistant Project Manager - Cardiovascular Projects", which stated that "This is an international postgraduate training service from Servier Laboratories Ltd" and described the authorship of the articles. A list of contributing authors was also given. There was an advertisement for Coversyl 4mg on the back page and a statement about the location of prescribing information appeared on page 2.

Servier did not accept that this item could be considered disguised promotional material and denied a breach of Clause 10.1. of the Code.

**PANEL RULING**

The Panel considered that the title of the mailing "Highlights From ... The European Cardiologist Journal by Fax" gave the impression that it contained extracts from an independently produced journal. In this regard the Panel noted that the letter from the assistant project manager stated that the articles themselves were totally independent. In the Panel's view some readers would assume that the mailing was part of an abstracting, or similar, service. This impression was strengthened by the statement on the front cover "Provided as a service to medicine by Servier Laboratories". Although Servier in its response had consistently referred to "The European Cardiologist - Journal by Fax", there was no hyphen between the words "Cardiologist" and "Journal" on the front cover of the mailing and this made the meaning of the title somewhat ambiguous.

The Panel noted that the papers published in the mailing were written at the invitation of Servier International. The authors came from an international group of 41 contributors listed on the inside front cover. The Panel did not consider that the mailing adequately explained the origin of the papers. In the Panel's view, readers of the material might regard the papers differently if they knew how they had been generated.

The Panel noted Servier's view that the mailing had clearly been presented as promotional material. The Panel did not consider, however, that the role of the company in the generation of the papers had been made sufficiently clear. It appeared as if Servier was offering an abstracting service from a recognised clinical journal which was not so.

In the Panel's view, this constituted disguised promotion and a breach of Clause 10.1 was ruled.

**Complaint received** **15 June 1998**

**Case completed** **13 August 1998**

---

**AUTH/722/6/98**

# GENERAL PRACTITIONER v ASTRA

## Imdur mailing

**A general practitioner complained about a mailing for Imdur (isosorbide mononitrate (ISMN) in an extended release formulation) issued by Astra. The complainant referred to a graph comparing the plasma concentrations of ISMN plain tablets 20mg bd with Imdur 60mg once daily for 0 to 24 hours after delivery. Between approximately 2 and 6 hours the plasma concentration for Imdur was greater than that for the plain tablets. The plasma concentration for the plain tablets did not fall below 1000nmol/l between two and six hours. The space between the two lines on the graph was shaded orange and labelled "Risk of underprotection". The complainant stated that the shaded area was a piece of scientific gobbledegook. In his view the only risk occurred when the plasma concentration fell below the therapeutic level, which was conveniently omitted from the graph. If the therapeutic level was below 1000 nmol/l there was clearly no underprotection with either of the regimes until about fourteen hours. The graph really was meaningless but was included to show a purported benefit which did not, in the complainant's view, exist.**

**The Panel noted that the therapeutic level had not been shown on the graph and that Astra had submitted that there were no published data on accepted minimum therapeutic levels for nitrates in the treatment of angina. The shaded area of the graph highlighted the differences in plasma concentration between Astra's product Imdur and ISMN 20mg bd and the Panel considered that it was misleading to label this section as "Risk of underprotection" and to refer to possible underprotection with a bd nitrate when there were no accepted minimum therapeutic levels. The Panel noted Astra's submission that undertreatment during the first 8 hour period correlated with the risk of having an ischaemic episode and therefore reflected the risk of underprotection irrespective of the concept of a general "therapeutic level". This data appeared on page 1 of the mailing. The Panel did not accept that readers would necessarily link the graph on page 1 with the graph in question which appeared on page 3. The Panel considered that the graph and the claim "Underprotection possible with a b.d. nitrate" were misleading and a breach of the Code was ruled.**

A general practitioner submitted a complaint about a mailing about Imdur (isosorbide mononitrate in an extended release formulation) (ref IMD 3316) sent by

Astra Pharmaceuticals Ltd to general practitioners in the UK.

The mailing, referred to the use of Imdur in angina and consisted of a four page leaflet, a "Dear Doctor" letter and a reply paid card. The complaint concerned page 3 of the leaflet headed "And avoiding nitrate tolerance" with the sub heading "Underprotection possible with a b.d. nitrate", below which was a graph which plotted plasma concentration nmol/l against hours after nitrate administered. The graph compared data for ISMN (isosorbide mononitrate plain tablets) 20mg bd, with that for Imdur 60mg once daily. The graph showed that after each dose of the ISMN 20mg tablets, administered at 0 and what appeared to be 6 hours, plasma levels of ISMN rose sharply but also fell sharply between the two doses. Plasma levels of ISMN from once daily Imdur, administered at 0 hours, rose more slowly than with the tablets, peaked at approximately 5 hours, before declining. Between approximately 2 and 6 hours the plasma concentration of ISMN resulting from Imdur was greater than that resulting from the tablets. At this point the space between the two lines on the graph was shaded orange and labelled "Risk of underprotection".

## COMPLAINT

The complainant referred to the shaded area in the graph labelled "Risk of underprotection" and stated that this was a piece of scientific gobbledegook. In the complainant's view the only risk occurred when the plasma concentration fell below the therapeutic level, which was conveniently omitted from the graph. If this was below 1000 nmol/l there was clearly no underprotection with either of the regimes until about fourteen hours. The graph really was meaningless but was included to show a purported benefit which did not, in the complainant's view, exist.

## RESPONSE

Astra stated that a graph on page 1 of the leaflet had been adapted from two studies (Carboni *et al* (1987) and Jonsson (1990)). This showed firstly the number of ischaemic episodes over a 24 hour period in patients with stable effort angina who were on no medication except sublingual nitroglycerin for relief of anginal symptoms, and secondly the plasma concentration profile of Imdur in healthy volunteers, again over a 24 hour period. This highlighted the number of both symptomatic and asymptomatic ischaemic episodes in the patients of which the greatest number clearly occurred in the morning (during the 8 hour window 7am to 3pm). When Imdur was taken in the morning, as shown graphically, the high plasma levels of nitrate coincided with the peak times of occurrence of ischaemic episodes. During this period, plasma nitrate concentrations fell broadly between the range of 1000 and 2750 nmol/l.

Page 3 of the leaflet depicted the findings of the Olsson and Allgén study (1992) graphically and reflected figure 1 of the publication. This showed the plasma concentrations of Imdur once daily and ISMN tablets 20mg, twice daily, over the 24 hour period following nitrate administration. Unlike the plasma concentration of Imdur, that of 5-ISMN was shown to fluctuate over the critical first 8 hour period after morning nitrate administration when ischaemic risk had been shown to be at its greatest (from page 1 of the leaflet). A further factor to consider was that an abrupt drop and removal of nitrate plasma concentration might be undesirable as this might theoretically increase the likelihood of rebound phenomena (Olsson (1992)). The orange shaded area therefore corresponded to this potential shortfall of plasma nitrate when comparing an asymmetrical twice daily dosing regimen of ISMN to once daily therapy with Imdur over the first 8 hour period (as shown on page 1 of the leaflet). Under-treatment during this period correlated with the risk of having an ischaemic episode and therefore reflected the risk of under protection irrespective of the concept of a general "therapeutic level".

The graph on page 3 was therefore, a sequitur to page 1 of the leaflet. This graph was headed "Underprotection possible with a b.d. nitrate". The intention of this was to explain the relative underprotection that twice daily therapy with ISMN offered compared to the once daily therapy with Imdur as represented on the graph. The orange shaded area was therefore substantiated from the evidence both presented and referenced and Astra submitted that the graph was clear, fair and balanced.

The graphical format had been used since 1996 to an audience of secondary care physicians which included consultant cardiologists. Astra believed that the use of this representation of data to a specialist audience without adverse comment further supported the company's view that the representation was clear, fair and balanced.

Astra submitted that with regard to the therapeutic level it was widely accepted that inter individual variability occurred between patients in their nitrate plasma levels achieved and there were no published data that it was aware of on accepted minimum therapeutic levels required for nitrates in the treatment of angina. Therefore it was not possible to present a single meaningful target plasma concentration.

Although plasma levels of nitrates after both Imdur and ISMN 20mg bd fell below 1000 nmol/l after about 14 hours, as pointed out by the complainant, this was of relatively little clinical concern in the light of the data presented on the timing of ischaemic episodes.

In summary, the company submitted that graph on page 3 of the leaflet was based on an evaluation of the available evidence, it did not mislead either directly or by implication and was clear, fair and balanced. Astra denied any breach of Clause 7.2 and 7.6 of the Code.

## PANEL RULING

The Panel examined the relevant page of the leaflet. It noted that a therapeutic level had not been shown on the graph and Astra's submission that there were no published data on accepted minimum therapeutic levels required for nitrates in the treatment of angina.

The Panel noted that the shaded area of the graph highlighted the differences in plasma concentration between Astra's product Imdur and ISMN 20mg bd. The Panel considered that it was misleading to label this section as "Risk of underprotection" and to refer to

possible underprotection with a bd nitrate when there were no accepted minimum therapeutic levels.

The Panel noted Astra's submission that undertreatment during the first 8 hour period correlated with the risk of having an ischaemic episode and therefore reflected the risk of underprotection irrespective of the concept of a general "therapeutic level". The Panel did not accept that readers would necessarily link the graph on page 1 with the graph in question which appeared on page 3.

The Panel considered that the graph and the claim "Underprotection possible with a b.d. nitrate" were misleading. A breach of Clause 7.2 of the Code was ruled.

**Complaint received** 16 June 1998

**Case completed** 3 August 1998

---

**CASE AUTH/723/6/98**

# HOECHST MARION ROUSSEL v UCB PHARMA

## Promotion of Zirtek

**Hoechst Marion Roussel complained about a Zirtek (cetirizine) detail aid issued by UCB Pharma. Hoechst Marion Roussel alleged that a number of claims beginning "No other antihistamine ..." were exaggerated, all-embracing and ambiguous but the Panel considered that such claims need not necessarily be in breach of the Code and each such claim would have to be considered on its merits.**

**The claim "No other antihistamine generates more power" headed a page which featured a schematic view of the early and late phases of allergic inflammation but, in the Panel's view, readers would not necessarily relate the claim to the diagram below. The Panel considered that the claim would be seen as relating to efficacy and implying that no other antihistamine was more efficacious. Such a claim would require direct comparative data. The Panel considered that it was ambiguous and implied a special merit which had not been substantiated and ruled it in breach.**

**A page headed "No other antihistamine has a broader safety profile" examined various safety aspects of Zirtek compared with other antihistamines. The Panel noted that the claim was above a table which compared various properties of selected antihistamines - Zirtek, terfenadine, loratadine and fexofenadine. Within the category of non-sedating antihistamines astemizole and acrivastine had not been included. The Panel considered that given the data printed below the claim it was misleading and exaggerated and ruled it in breach. A breach was also ruled in relation to the claim "Zirtek has an excellent safety profile as acknowledged by EAACI". It did not reflect the views of the authors of the EAACI (European Academy of Allergy and Clinical Immunology) position paper. That paper concluded that the "new antihistamines appear to be useful and relatively safe ..." but there was no specific endorsement of cetirizine.**

**On the same page of the detail aid was tabled information which Hoechst Marion Roussel alleged disparaged its product fexofenadine. By juxtaposition of information regarding fexofenadine's interaction with ketoconazole and erythromycin directly beneath the heading on safety and in the same position in the table as information on terfenadine's interactions, Hoechst Marion Roussel considered that the objective was to imply that this interaction represented a safety issue with respect to fexofenadine. The Panel considered that the statement regarding interactions with fexofenadine was not sufficiently clear and gave a misleading impression. Prescribers might be led to avoid prescribing fexofenadine with ketoconazole or erythromycin whereas it was an option. The table disparaged fexofenadine and was misleading and was ruled in breach.**

Hoechst Marion Roussel Ltd complained about promotional materials for Zirtek (cetirizine) issued by UCB Pharma Limited. The company made specific allegations only about certain claims which were made in the Zirtek detail aid (ref UCB-Z-98-02) but stated that it was aware that these claims also appeared in other formats.

### 1 Claims beginning with "No other antihistamine ..."

#### COMPLAINT

Hoechst Marion Roussel's overriding objection was to UCB's use of claims beginning "No other antihistamine ...".

Hoechst Marion Roussel alleged that these claims were exaggerated, all-embracing and ambiguous and thus in breach of Clauses 7.2 and 7.8. They could be taken to imply special attributes and merits of cetirizine which Hoechst Marion Roussel did not believe had been substantiated by any data so far presented by UCB and nor did Hoechst Marion Roussel consider it likely that such claims were capable of substantiation. A breach of Clause 7.3 of the Code was alleged.

In order to substantiate claims of this nature Hoechst Marion Roussel considered that, as a minimum, comparative data were required with other non-sedating antihistamines. The company did not consider adequate comparative data existed and particularly not in relation to its product fexofenadine.

#### RESPONSE

UCB said that it did not suggest any superlative qualities or infer any special merits or attributes for cetirizine. The intent behind claims in the detail aid beginning with "No other antihistamine ..." was merely to imply that no other antihistamine currently on the market surpassed cetirizine. Accordingly, UCB had not breached Clauses 7.2 or 7.8 of the Code. Nor had it breached Clause 7.3 in that it had not found articles in the literature which would clearly indicate that any other antihistamine surpassed cetirizine in the relevant respects. UCB had asked Hoechst Marion Roussel to provide such evidence which, on both occasions, it refused to do. Without exception, each page on which a claim appeared also

included supporting rationale.

**PANEL RULING**

The Panel considered that claims starting with "No other antihistamine ..." need not necessarily be in breach of the Code. Each claim would have to be considered on its own merits. In the Panel's view the aim of the detail aid was to compare Zirtek with other non-sedating antihistamines. There were, however, older, sedating antihistamines available. The Panel considered that, in the absence of any qualification to the contrary, claims beginning with "No other antihistamine ..." would have to take account of all available antihistamines.

The Panel ruled no breach of the Code with regard to claims beginning with "No other antihistamine" *per se* but noted that Hoechst Marion Roussel had made specific allegations about particular claims and these were dealt with below (points 2 and 3).

**2 "No other antihistamine generates more power"**

This claim appeared as the heading to page 1 of the detail aid and appeared above a schematic representation of the early phase and late phase of allergic inflammation.

**COMPLAINT**

Hoechst Marion Roussel alleged that the claim that "No other antihistamine has more power" must be considered as highly ambiguous and potentially misleading. "Power" as a concept relating to antihistamines was not defined in the piece, nor were any grounds for claiming superiority (or even equivalence) to other antihistamines adequately substantiated either in the detail aid or subsequently in correspondence with UCB. Hoechst Marion Roussel therefore alleged this statement to be in breach of Clauses 7.2, 7.3 and 7.8.

**RESPONSE**

UCB did not consider that the claim was ambiguous. The claim was used in the context of a detail aid which addressed allergic inflammation and it was a well accepted fact that this specific form of inflammation had two phases, namely an early histamine-led reaction and a late cellular infiltrate reaction. Cetirizine had been shown to have an action on both phases and hence reduced the importance of allergic inflammation. It was evident that the use in the detail aid of the claim referred to cetirizine's powers with respect to these reactions. UCB added that the Oxford Concise, Oxford Short Form and Collins Dictionaries defined power as "the ability to do something". UCB therefore rejected the allegation that it was in breach of Clauses 7.2, 7.3 or 7.8 or the Code.

**PANEL RULING**

The Panel noted that Hoechst Marion Roussel had complained about the claim "No other antihistamine has more power" whereas the claim in the detail aid read "No other antihistamine generates more power".

The Panel noted that the claim headed a page which featured a schematic view of the early and late phases of allergic inflammation. There was no other topic discussed on the page and in the Panel's view readers would not necessarily relate the claim to the diagram below. The Panel noted UCB's submission that "power" was defined as the ability to do something. In the Panel's view, however, the phrase "... generates more power" was more likely to be interpreted as "force". The Panel considered that such an interpretation would lead to the claim being seen to relate to efficacy and implying that no other antihistamine was more efficacious than Zirtek. Such a claim would require direct comparative efficacy data for substantiation. The Panel considered that the claim was ambiguous and that it had not been substantiated and ruled a breach of Clauses 7.2 and 7.3 of the Code. The Panel considered that the claim implied a special merit which had not been substantiated. A breach of Clause 7.8 was ruled.

**3 Safety Profile**

Page three of the detail aid examined various aspects relating to the safety of Zirtek compared with other antihistamines.

**COMPLAINT**

Hoechst Marion Roussel also strongly objected to UCB's use of claims relating to safety on page 3 which was headed, "No other antihistamine has a broader safety profile."

Hoechst Marion Roussel stated that apart from the questionable use of the word "safety" (Clause 7.7), it considered that the claim "EAACI has acknowledged Zirtek's excellent safety profile" was an exaggeration. The data used to support this statement were taken from a position paper published by the European Academy of Allergy and Clinical Immunology (EAACI) (Passalacqua *et al* (1996)) which merely reviewed the data on the newer antihistamines and acknowledged the favourable risk/benefit ratio of those agents whilst noting that careful case-by-case evaluation was still required. This hardly seemed to be 'acknowledging an excellent safety profile' and certainly was by no means specific to cetirizine. Furthermore, the paper reviewed the newer antihistamines from three tolerability perspectives, namely: arrythmogenic effect, carcinogenicity and sedation. Whilst cetirizine was not associated with concerns regarding the first two aspects, as was mentioned in the Passalacqua *et al* review, there existed evidence of sedation with cetirizine from certain studies. With regard to antihistamine usage, sedation was an important aspect of general safety since a broad population of users now needed to be able to carry out normal activities such as driving a car or operating machinery. Whilst Hoechst Marion Roussel recognised that cetirizine was generally well-tolerated, it considered that the claim of an "... excellent safety profile as acknowledged by EAACI" was misleading and exaggerated (Clause 7.2).

**RESPONSE**

With regard to the use of the word "safety" UCB assumed that Hoechst Marion Roussel was referring to the requirement in Clause 7.7 of the Code that the word 'safe'

must not be used without qualification. On the page where the statement "No other antihistamine has a broader safety profile" appeared, there were at least five such qualifications/explanations:

(1) reference to the EAACI position paper by Passalacqua *et al*;

(2) a medicine interactions table which reproduced the potential for drug interactions described in the data sheets of several currently available antihistamines including cetirizine;

(3) a statement indicating cetirizine was not extensively metabolised by the liver;

(4) a statement indicating cetirizine's lack of cardiotoxicity in that it did not induce QTc interval prolongation;

(5) a statement indicating loratadine's propensity to block human cardiac K v1.5 (potassium channels) as well as that seen with terfenadine.

UCB noted that Hoechst Marion Roussel considered that the use of the EAACI position paper would be inappropriate since it considered that this paper did not acknowledge cetirizine's safety.

UCB stated that the paper reviewed comprehensively the tolerability of second generation antihistamines in three respects – arrythmogenic effect, carcinogenicity and sedation. Hoechst Marion Roussel objected to the use of the word "acknowledges" with regard to the paper's position on the safety of cetirizine. UCB submitted that the word "acknowledge" in the Oxford Concise, Oxford Short Form and Collins Dictionaries was defined as "to recognise or admit the existence truth or reality of" or "to admit that something is true or valid". UCB considered that this word was entirely suitable.

In earlier correspondence with Hoechst Marion Roussel, UCB acknowledged that the word "excellent" was not in the text of Passalacqua *et al* but the company considered that it was a fair reflection of the authors' views. Following their categorisation of safety parameters, UCB considered that the following quotations both reflected the authors' overall meaning and justified the claim:

Sedative effects: "As for cetirizine, in two placebo-controlled studies, Gengo *et al* demonstrated that 5, 10 and 20mg did not impair psychomotor and driving performance as compared to 25mg hydroxyzine or diphenhydramine 50mg."

Arrythmogenic effects: "Finally, to date, there are no case reports of adverse cardiac events by acrivastine, azelastine, cetirizine, or ketotifen."

Carcinogenicity: "An increase in tumor growth was greatest for astemizole and loratadine, followed by hydroxyzine, while doxylamine and cetirizine were comparable to placebo."

UCB objected to the inference in Hoechst Marion Roussel's letter that the EAACI review was in any way cursory in this regard.

**PANEL RULING**

The Panel considered that the claim "No other antihistamine has a broader safety profile" implied a comparison with all other antihistamines. The Panel noted that the claim was above a table which compared various properties of selected antihistamines – Zirtek, terfenadine, loratadine and fexofenadine. Within the category of non-sedating antihistamines astemizole and acrivastine had not been included. The Panel considered that given the data presented below the claim it was misleading and exaggerated. Breaches of Clauses 7.2 and 7.8 were ruled.

The Panel noted that the EAACI position paper by Passalacqua *et al* was a review of data on the safety of the newer, non-sedating antihistamines and their risk/benefit ratios. The authors listed those newer antihistamines which were either commercially available or undergoing clinical trials. Fexofenadine was not listed and nor was any reference to it made in the paper. For those antihistamines listed the authors reviewed data relating to sedation, arrhythmogenic effect and carcinogenicity. The Panel noted that with regard to sedation certirizine was not the only antihistamine which had been reported not to affect psychomotor performance at therapeutic doses in comparison to an active control and conversely some workers had reported that cetirizine was associated with sedation. The paper suggested that a rigorous double blind study of the potential sedative effects of antihistamines should be carried out. As acknowledged by UCB certirizine was not the only antihistamine for which there were no case reports of adverse cardiac events. The paper stated that cetirizine and acrivastine together with loratadine appeared to be the least likely to be arrhythmogenic. The results relating to carcinogenicity involved a study in mice. Passalacqua *et al* stated such events were "not immediately transferable to man" and that, in clinical terms, no report of carcinogenicity had been published during more than 50 years of clinical trials and clinical use of antihistamines. The conclusion of the paper was that the "newer antihistamines appear to be useful and relatively safe ...". There was no specific endorsement regarding the safety profile of certirizine. The Panel considered, therefore, that the claim "Zirtek has an excellent safety profile as acknowledged by EACCI" was misleading as it did not reflect the views of the authors. A breach of Clause 7.2 was ruled.

## 4 Tabular Information

**COMPLAINT**

Hoechst Marion Roussel was also concerned about the tabular information on page 3 which it alleged was disparaging of its product fexofenadine in breach of Clause 8.1. By juxtaposition of the information regarding fexofenadine's interaction with ketoconazole and erythromycin directly beneath the heading on safety and in the same position in the table as information on terfenadine's interactions, the objective was to imply that this interaction represented a safety issue with respect to fexofenadine. That this was indeed the intention was implicit in a letter to Hoechst Marion Roussel from UCB in which was stated, "... it would be misleading to omit this real risk".

In fact, there were no known clinical consequences of the interaction between fexofenadine and ketoconazole or

erythromycin, as was clear from the summary of product characteristics (SPC), nor was there any contra-indication to their concomitant use, as there was with terfenadine. Hoechst Marion Roussel believed therefore that the intention of the table was to mislead the prescriber as to the safety profile of fexofenadine. The clear implication of the piece was that similar safety issues existed with fexofenadine with respect to concomitant use with ketoconazole or erythromycin as occurred with terfenadine, where there was a well-described interaction which could, albeit rarely, lead to cardiotoxicity due an established mechanism. The data sheet for Triludan (terfenadine) was provided for information.

There was convincing evidence that this was not an issue with fexofenadine and Hoechst Marion Roussel felt most strongly therefore that the information as presented by UCB was both misleading (Clauses 7.2 and 7.6) and disparaging (Clause 8.1).

## RESPONSE

UCB submitted that the table was comprised of three elements describing (i) antihistamine class, (ii) potential for hepatic metabolisation and (iii) potential for drug interactions. Elements (ii) and (iii) of the table simply reproduced data from the stated products' SPCs. Fexofenadine's SPC clearly stated in section 4.5: "Co-administration of fexofenadine hydrochloride with erythromycin or ketoconazole has been found to result in a 2-3 times increase in the levels of fexofenadine in the plasma".

UCB failed to see how it could have breached Clause 8.1 of the Code in this respect.

## PANEL RULING

The Panel noted that the table listed those interactions currently included on the data sheets/SPCs for Zirtek, terfenadine, loratadine and fexofenadine. There were a number of medicines listed under terfenadine which were either contra-indicated in patients taking terfenadine or for which the concomitant use was not recommended. Two of the medicines which were contra-indicated in patients taking terfenadine were ketoconazole and erythromycin. The Panel understood that the use of either of these two medicines in conjunction with terfenadine could lead to serious adverse cardiac events due to increased plasma levels of terfenadine. Ketoconazole and erythromycin were also listed under fexofenadine, an antihistamine closely related to terfenadine. Although fexofenadine interacted with ketoconazole and erythromycin the SPC stated that the resultant increases in fexofenadine plasma levels had not been accompanied by any effects on the QT interval and were not associated with any increase in adverse events compared with the medicines given singly.

The Panel considered that in the light of the well known interactions with terfenadine the statement regarding the interactions with fexofenadine was not sufficiently clear. It gave a misleading impression as to the nature and consequence of the interaction between fexofenadine and ketoconazole or erythromycin. The statement might lead prescribers to avoid prescribing fexofenadine with either of these two medicines whereas it was a feasible option. The statement did not convey the fact that as stated in the SPC there was no additional clinical consequences of prescribing fexofenadine with either ketoconazole or erythromycin over and above those associated with prescribing each one singly. The Panel considered that the table disparaged fexofenadine and was misleading as it did not accurately reflect the position. Breaches of Clauses 8.1 and 7.2 were ruled.

**Complaint received** **17 June 1998**

**Case completed** **7 September 1998**

CASE AUTH/724/6/98

# GLAXO WELLCOME v MERCK SHARP & DOHME

## Information on montelukast in Pharmatrak

**Glaxo Wellcome complained about Merck Sharp & Dohme's promotional use of an issue of Pharmatrak entitled "Evaluated Information on Montelukast A Newly Launched Product". Pharmatrak was published by the Pharmacy Practice Division of the Common Services Agency for the National Health Service in Scotland.**

**Glaxo Wellcome noted that a claim made for montelukast was "... significant benefit compared with salmeterol in a short-term unpublished study in patients with exercise-induced brochoconstriction". No reference was given but the company presumed it referred to a study in which Glaxo Wellcome's Serevent (salmeterol) was compared with montelukast used as monotherapy over eight weeks. Glaxo Wellcome was unclear as to whether montelukast was licensed in the UK as monotherapy in exercise-induced bronchoconstriction but whether it was or not salmeterol was not licensed as monotherapy and Glaxo Wellcome alleged that the claim was unfair. Glaxo Wellcome also considered that the claim was not balanced as the vast majority of studies that had been performed looking at salmeterol in exercise-induced bronchoconstriction, albeit with different methodology, usually single dose versus chronic dosing, showed it to be an extremely effective treatment in that condition. The Panel noted that use of the document by Merck Sharp & Dohme for promotional purposes brought it within the scope of the Code. Merck Sharp & Dohme had accepted that the comparison was inappropriate. The Panel considered that the claim was misleading and not a balanced reflection of the evidence and a breach was ruled.**

**Glaxo Wellcome also complained about a statement that montelukast was indicated as add-on to inhaled corticosteroids in Step 3 of the British Thoracic Society Guidelines alleging that this was inaccurate and misleading. The Guidelines stated in a page devoted to antileukotrienes that more studies were needed to provide comparative data against established therapies before any positioning recommendation could be made. They were not mentioned at Step 3 or indeed any other step. The Panel noted that Merck Sharp & Dohme accepted that the statement at issue had been one of opinion rather than fact. A breach of the Code was ruled.**

Glaxo Wellcome complained about Merck Sharp & Dohme's promotional use of an issue of Pharmatrak entitled "Evaluated Information on Montelukast A Newly Launched Product". Pharmatrak was an independent publication produced by the Pharmacy Practice Division of the Common Services Agency for the National Health Service in Scotland. The front cover of the issue of Pharmatrak in question, dated 20 January 1998, stated that it had been distributed by Merck Sharp & Dohme with permission from the Pharmacy Practice Division. There was also a boxed statement on the cover which said that the document was not to be used for commercial purposes. Page one of the document presented brief product information on montelukast including the name Singulair and the fact that it was a leukotriene receptor antagonist. There then followed six clinical "key points". Pages 2 to 4 gave details of efficacy and safety.

### COMPLAINT

Glaxo Wellcome noted the statement on the front cover that Pharmatrak was "Not to be used for commercial purposes" but submitted that this would however appear to be exactly the case and the company was aware of representatives using it for strong promotional messages in support of montelukast. Glaxo Wellcome was unclear whether that would in itself constitute a breach of Clause 9.5 of the Code or whether it would still be in breach even if permission had been received.

Glaxo Wellcome noted that the fourth key point for montelukast given on page 1 was "... significant benefit compared with salmeterol in a short-term unpublished study in patients with exercise-induced bronchoconstriction." No reference was given to this but the company presumed it referred to data presented at the American Thoracic Society meeting in Chicago, April 1998. In the study Serevent (salmeterol) was compared with montelukast used as monotherapy over eight weeks. This was clearly using Glaxo Wellcome's product, if not montelukast, out of licence. Glaxo Wellcome was unclear whether in fact montelukast was licensed in the UK as monotherapy in exercise-induced bronchoconstriction and awaited Merck Sharp & Dohme's and the Medicines Control Agency's clarification. However, whether montelukast was licensed or not, salmeterol was not licensed as monotherapy and Glaxo Wellcome alleged that the claim was certainly unfair and therefore in breach of Clause 7.2 of the Code. The company also considered that the claim was not balanced as the vast majority of studies that had been performed looking at salmeterol in exercise-induced bronchoconstriction, albeit with different methodology usually of single dose versus chronic dosing, showed it to be an extremely effective treatment in exercise-induced bronchoconstriction. The company alleged a breach of Clause 7.2 of the Code.

Glaxo Wellcome also noted the first key point, which stated that montelukast was indicated as add-on to inhaled corticosteroids in Step 3 of the British Thoracic Society (BTS) Guidelines. This was inaccurate and misleading. The company drew attention to the most recent version of the Guidelines, published in Thorax in February 1997 and in particular to a paragraph devoted to antileukotrienes suggesting that "more studies are needed to provide comparative data against established therapies before any positioning recommendation can be made". The step-wise managment plan often reproduced for doctors in their clinics and surgeries included no mention of leukotriene receptor antagonists at Step 3 or indeed at any other step. Glaxo Wellcome alleged that this key point, and its use for promotional purposes was a further breach of Clause 7.2 of the Code.

### RESPONSE

Merck Sharp & Dohme stated that after considering the two allegations of a breach of Clause 7.2 it would have to

accept these breaches, and also accept a finding of a breach of Clause 9.5 of the Code.

The company, however, offered some further background information to set these matters in the correct context which it believed offered some mitigation in this matter. Merck Sharp & Dohme noted that once again it had been denied the opportunity to resolve this matter informally with Glaxo Wellcome before the issue became a matter of formal complaint. Given its acceptance of the allegation Merck Sharp & Dohme considered that this was particularly unfortunate.

Merck Sharp & Dohme explained that originally the company was approached by the Pharmacy Practice Division (PPD) to comment on the accuracy of its document, "Evaluated Information on Montelukast "A Newly Launched Product" from a medical perspective. This was duly done by the company's medical department, and certain issues clarified. As this was viewed as an independent third party document, it was not subject to any formal medical/legal review of the final text. It was PPD's decision when to publish, and what to publish.

Merck Sharp & Dohme stated that some time after that medical comment on the document, members of the sales department, and others, met PPD and it was agreed that the company would purchase 1000 reprints. It was Merck Sharp & Dohme's understanding that PPD had come to a similar arrangement with other pharmaceutical companies for other editions of "Pharmatrak". It was also the company's understanding that it had been agreed by PPD that Merck Sharp & Dohme could distribute these to "... the relevant people as necessary". However, it appeared that both parties left with a different interpretation as to precisely what that phrase meant. The wording of the rider which allowed Merck Sharp & Dohme to "distribute" the document "... with the permission of PPD" was not reviewed by the company and it was regrettable that this opportunity for clarification was missed. The company submitted that it had acted in good faith as it considered at that stage that it had the requisite permission to satisfy Clause 9.5. The company now accepted that it did not have the required clarity of written permission and, therefore, admitted a breach of Clause 9.5.

Merck Sharp & Dohme accepted that the comparison with salmeterol was inappropriate in a piece which was subsequently used promotionally. However, at the time the document was reviewed medically (as an independent third party publication) it was not intended to be used promotionally. In the circumstances, the company, admitted a breach of Clause 7.2.

Merck Sharp & Dohme submitted, with regard to the statement as to the positioning of montelukast at Step 3 of the BTS Guidelines, that this was an expression of opinion on the part of the company as to the correct positioning of montelukast, rather than fact. This opinion was given when the document was an independent third party document. In the circumstances the company admitted a breach of Clause 7.2. Merck Sharp & Dohme gave an unequivocal assurance that this document would not be used for future promotional purposes.

## PANEL RULING

The Panel noted that Clause 9.5 of the Code prohibited the reproduction of official documents for promotional purposes unless permission had been given in writing by the appropriate body. The Panel noted that Merck Sharp & Dohme had purchased 1000 copies of Pharmatrak and had received permission from the Pharmacy Practice Division to distribute them to ".... relevant people as necessary". The company had purchased reprints and had not copied or duplicated the document. Previously "official documents" had been taken to be prescription forms (FP1Os) and the like. The Panel queried whether Pharmatrak would be an official document as meant by Clause 9.5. The Panel noted that Glaxo Wellcome had raised the issue but had not made an allegation as such so there was no need for the Panel to rule upon it. The Panel noted that although the document had been independently produced, Merck Sharp & Dohme's use of it for promotional purposes brought it within the scope of the Code.

The Panel noted Merck Sharp & Dohme's submission, with regard to the claim "Montelukast showed significant benefit compared with salmeterol in a short-term unpublished study in patients with exercise-induced bronchoconstriction", that this comparison was inappropriate although no explanation had been given. Glaxo Wellcome had complained that the comparison was misleading because it involved the use of Serevent (salmeterol) as monotherapy which was contrary to its licensed use. Neither company provided a copy of the study at issue. The Panel decided that the claim was misleading as it was either referring to the use of salmeterol as monotherapy or because it failed to make it clear that salmeterol had been used as add on therapy. The Panel had no way of knowing if the results from the particular study used were representative of the efficacy data for salmeterol. Glaxo Wellcome alleged that the results were not balanced and this had not been disputed by Merck Sharp & Dohme. Further Merck Sharp & Dohme had accepted that the comparison with salmeterol was inappropriate in a piece which was subsequently used promotionally. The Panel considered that the claim was misleading and was not a balanced reflection of the evidence and therefore ruled a breach of Clause 7.2.

The Panel noted that one of the key points had stated that montelukast was "... indicated as an add-on to inhaled corticosteroids in Step 3 of the BTS Guidelines" which was not so. To state otherwise was misleading and a breach of Clause 7.2 of the Code was ruled as acknowledged by Merck Sharp & Dohme.

**Complaint received** **19 June 1998**

**Case completed** **6 August 1998**

CASE AUTH/726/6/98 *NO BREACH OF THE CODE*

# MERCK SHARP & DOHME v GLAXO WELLCOME

## Serevent advertisements

**Merck Sharp & Dohme complained about a full advertisement and two abbreviated advertisements for Serevent issued by Glaxo Wellcome alleging that the claim "... Serevent controls my asthma symptoms" implied monotherapy whereas the summary of product characteristics stated that "patients with asthma should normally also be receiving regular and adequate doses of inhaled anti-inflammatory agents ...or oral corticosteroids".**

**In the Panel's view the impression given by both the full advertisement and the abbreviated advertisement was that Serevent alone controlled asthma. This impression was not negated by the inclusion of the prescribing information in the full advertisement. The Panel considered that both types of advertisement were misleading given the restrictions on the use of Serevent and each was ruled in breach of the Code.**

**Upon appeal by Glaxo Wellcome, the Appeal Board noted that the advertisements referred to symptom control and did not refer to inflammation. The company's submission that Serevent was promoted in line with the British Guidelines on Asthma Management was noted. The Guidelines were well known and used by general practitioners; Serevent was a well established product. In the circumstances the Appeal Board did not consider the advertisements misleading and no breach of the Code was ruled.**

### COMPLAINT

Merck Sharp & Dohme submitted a complaint about the current campaign for Serevent (salmeterol) by Allen & Hanburys Limited. Merck Sharp & Dohme alleged that the claim "...Serevent controls my asthma symptoms" clearly implied monotherapy, whereas the summary of product characteristics (SPC) stated that "...patients with asthma should normally also be receiving regular and adequate doses of inhaled anti-inflammatory agents (eg corticosteroids, and/or in children, sodium cromoglycate), or oral corticosteroids...". Breaches of Clauses 3.2 and/or 7.2 and/or 7.8 were alleged.

Merck Sharp & Dohme stated that it had tried to resolve this with Glaxo Wellcome and the relevant correspondence was provided. Glaxo Wellcome's defence of the original advertisement was that the prescribing information resolved any ambiguity. Merck Sharp & Dohme did not believe that this was an acceptable defence as it understood that promotional copy should be read literally and without recourse to prescribing information.

Merck Sharp & Dohme included two examples of abbreviated advertisements with the promotional claims "Serevent controls my asthma symptoms" and "I control my life", MIMS June 1998 and Prescriber, 5 June 1998, which did not have any prescribing information. In this context the prescriber would assume that Serevent could be used as monotherapy. Merck Sharp & Dohme alleged that the abbreviated advertisements were in breach of Clause 3.2 and/or Clauses 7.2 and/or 7.8.

### RESPONSE

Glaxo Wellcome submitted that there were now many studies looking at patients with asthma who remained symptomatic despite being on a dose of inhaled steroid. These patients often found that the level of symptoms affected their life. Many trials had evaluated the addition of Serevent in these patients. Similar trials at other doses of inhaled steroids had been done by other companies and the results were all similar - ie the addition of a long-acting bronchodilator, in this instance salmeterol, offered significant advantage over increasing the dose of inhaled steroids and in many cases brought the recalcitrant symptoms under control. For over eight years Glaxo Wellcome had been promoting the addition of Serevent to anti-inflammatory treatment (in practice, inhaled steroids) and in recent years the dose of Serevent to be added had reduced in line with the available evidence.

However, the company always maintained that it was prescribed in addition to anti-inflammatory treatment which should not be stopped or reduced when Serevent was added. This was consistent with the licence and the prescribing information.

Asthmatics who had symptoms and who regularly needed treatment were, by definition, on Step 2 of the British Guidelines on Asthma Management and were in receipt of anti-inflammatory treatment. If they were still symptomatic despite regular anti-inflammatory treatment, they went on to Step 3, where the Guidelines advocated either an addition of a long-acting bronchodilator such as salmeterol or higher dose of inhaled steroid. Glaxo Wellcome fully endorsed the British Guidelines on Asthma Management which were drawn up by numerous learned and interested parties after careful consideration of all the evidence. Step 1 of the Guidelines suggested that patients who had infrequent symptoms only and the most mild form of asthma should have regular short-acting bronchodilators alone.

The company denied that there was any suggestion to the prescribing physician by the claim "Serevent controls my asthma symptoms" that Serevent should be used as a monotherapy.

### PANEL RULING

The Panel noted that the complaint was two fold. Firstly with regard to an advertisement which included prescribing information and secondly with regard to the abbreviated advertisements in MIMS and Prescriber.

The Panel noted that the Serevent SPC stated that patients should normally also be receiving regular and adequate doses of inhaled anti-inflammatory agents (eg corticosteroids, and/or in children, sodium cromoglycate), or oral corticosteroids. Serevent was not a replacement for these treatments which should be continued at the same dose and not stopped or reduced when Serevent treatment was initiated. The Panel also

noted the warning in Section 4.4 of the SPC that Serevent was not a replacement for inhaled oral corticosteroids or sodium cromoglycate. Patients were warned not to stop such therapy or reduce it without medical advice.

In the Panel's view the impression of the full advertisement and the abbreviated advertisements was that Serevent alone controlled asthma. This impression was not negated by the inclusion of the prescribing information in the full advertisement. The Panel considered that the advertisements were too general given the restrictions for use of Serevent.

The Panel considered that both the full advertisement and the abbreviated advertisements were misleading. Each was ruled to be in breach of Clause 7.2 of the Code.

## APPEAL BY GLAXO WELLCOME

Glaxo Wellcome's position was that Serevent should be promoted within the British Guidelines on Asthma Management which positioned addition of Serevent at Step 3. The SPC mentioned that patients receiving Serevent should normally be on inhaled steroids, but the licence granted for Serevent in 1990 allowed for it to be used as monotherapy.

The British Guidelines on Asthma Management stated that stepwise care should be encouraged in the treatment of asthma. These guidelines represented a consensus of clinicians involved in the treatment of asthmatics and it was given that all asthmatics, other than those purely at the most mild end of the spectrum, should be receiving inhaled corticosteroids as the mainstay. The Guidelines suggested that inhaled steroids should be used only after intermittent and occasional use of short-acting bronchodilators failed to control these mild patients, and yet in none of the inhaled steroids' promotional material was this made explicit. They were licensed for the prevention of asthma and that was how they were promoted. The same premise was thus true for the advertising of Serevent.

Glaxo Wellcome submitted that the control of symptoms was not possible in many patients with the use of inhaled steroids alone. In such patients the addition of Serevent was significantly better than increasing the dose of inhaled steroid in terms of improvement in symptom control. This was not synonymous with asthma control.

In line with other medicines in other therapeutic classes, indeed in other disease areas, Glaxo Wellcome was promoting the use of Serevent in line with its licence. Although consensus guidelines suggested it should be used at certain stages, and Glaxo Wellcome supported these, they were not necessarily synonymous with the licence as granted by the Medicines Control Agency. Glaxo Wellcome was not aware that in other disease areas, the treatment of hypertension, medicines normally reserved for more severe and complicated hypertension must state exactly the recommended position and timing of their use in their promotional material.

Glaxo Wellcome believed there was much data to supports its contention that adding Serevent controlled symptoms better than increasing inhaled steroids and this was the main basis of its promotion of Serevent. The use of Serevent as monotherapy, however, was within its current licensed indication. Under these circumstances Glaxo Wellcome did not believe that it had been in breach of the Code.

The company submitted that Serevent was the first inhaled, long acting, selective $ß_2$ agonist and had been licensed in 1990. The management of asthma was made up of two components, the control of inflammation with steroids and the control of symptoms with $ß_2$ agonists. The advertisement aimed to profile those patients who, despite treatment with inhaled steroids, remained symptomatic.

The majority of health professionals were aware of the British Guidelines on Asthma Management. The company submitted that asthma was well managed in the UK and that the majority of general practitioners would introduce an inhaled steroid at an early stage.

## APPEAL BOARD RULING

The Appeal Board noted that the SPC for Serevent stated that patients should normally also be receiving regular and adequate doses of inhaled anti-inflammatory agents. The advertisements referred to symptom control and did not refer to inflammation. The Appeal Board noted the data referred to by Glaxo Wellcome and the company's submission that Serevent was promoted in line with the British Guidelines on Asthma Management. Step 3 of the Guidelines referred to either the addition of salmeterol to low dose inhaled steroids or the use of high dose inhaled steroids. The Appeal Board accepted that the Guidelines were well known and used by general practitioners. Serevent was a well established product. In the circumstances, the advertisements were not misleading. The Appeal Board therefore ruled no breach of the Code in relation to each advertisement.

The appeal was therefore successful.

**Complaint received** **19 June 1998**

**Case completed** **16 September 1998**

# DIABETES CHARITY v LILLY

## Humalog advertisement

**The co-chairman of a diabetic charity complained about an advertisement for Humalog (insulin lispro) issued by Eli Lilly. The advertisement showed a pizza beneath which was a Humalog cartridge and an insulin pen. The complainant accepted that the advertisement was theoretically only intended for health professionals but the underlying message might be passed to people with diabetes. The message was not in their interests and nor was it within the guidelines for healthy eating. Pizza was high in carbohydrate and in fat. Both of these foods were likely to result in an increase in weight which was not healthy for anyone and especially for people with diabetes. The advertisement would encourage greater use of the product as a result of unhealthy eating.**

**The Panel did not accept that the underlying message of the advertisement was to promote unhealthy eating and hence encourage the use of Humalog. The Humalog summary of product characteristics stated that its rapid onset of activity allowed Humalog to be given very close to mealtime. The bullet points at the bottom of the advertisement described Humalog as "An inject-and-eat insulin" which could "now be given before or after meals". The strapline at the bottom read "Bringing flexibility to life". In the opinion of the Panel, the intention of the advertisement was to associate the properties of Humalog with the demands of a busy, modern lifestyle. The Panel considered that the use of the illustration of a pizza was not unreasonable. No breach of the Code was ruled.**

The co-chairman of a diabetes charity submitted a complaint about an advertisement for Humalog (insulin lispro) issued by Eli Lilly & Company Limited. The advertisement was headed "Fast Food" and featured a picture of a pizza beneath which was a picture of a Humalog cartridge in an insulin pen followed by the strapline "Fast Response". The advertisement had appeared in Diabetic Medicine in May, June and July 1998, Diabetic Update in June 1998, and Practical Diabetes in May and June 1998.

### COMPLAINT

The complainant appreciated that whilst this advertisement was only, theoretically, being seen by health care professionals, the underlying message might well be passed on to people with diabetes. The message was not in the interests of people with diabetes and nor was it within the guidelines for healthy eating.

The issue was not one of 'fast food' necessarily being bad but a pizza was very high in carbohydrate so encouraged a larger dose of insulin and was also very high in fat because of the cheese content. Both of these facts were likely to result in an increase in weight which was not healthy for anyone and especially people with diabetes because of their susceptibility to long term complications such as heart disease.

For these reasons, the complainant alleged that the advertisement was inappropriate and not in the interests of the health and general well-being of people with diabetes. It was going against the guidelines for treatment of diabetes and encouraged greater use of the product as a result of unhealthy eating.

### RESPONSE

Lilly stated that diabetic patients would have the occasional "treat" and at times would not have access to food other than 'fast food'. As a result it was important for them to know that they were able to maintain control of their diabetes in these situations. A recent study "Pizza, Coke and Tiramisu" had confirmed that Humalog provided this flexibility to these patients.

Lilly addressed each of the issues raised by the complainant:

**a) "The issue was not one of fast food necessarily being bad but a pizza was very high in carbohydrate so encouraged a larger dose of insulin ..."**

There could be no doubt that pizza was high in carbohydrate. Nutritional information from the packaging for a pizza similar to the one illustrated in the advertisement gave the carbohydrate content as 26g/100g of which 2.5g/100g was sugar. This meant that most of the carbohydrate load provided by a pizza was in the form of complex carbohydrate.

Contrary to the commonly held beliefs carbohydrate was not a problem *per se* for the management of diabetes. Complex carbohydrate was broken down and absorbed much more slowly than refined sugar and was thus associated with lower post prandial glucose excursions and more prolonged glucose uptake. This resulted in more efficient energy utilisation and less harmful glucose disposal. Indeed the delayed uptake of glucose as carbohydrate was broken down made it easier for a normal post prandial blood glucose profile to be achieved using modern insulin formulations.

It had been known since the 1960s that high carbohydrate diets were not harmful to diabetic subjects and did not lead to an increase in lipids such as triglyceride (Betteridge (1990)).

Starch (complex carbohydrate) caused a lower plasma glucose and insulin response than equimolar quantities of glucose or sucrose. The form in which carbohydrates were eaten was important. As much as possible should be as polysaccharides (for example bread, potatoes and cereals) (Hadden (1990)).

Lilly submitted that pizza base, which was a form of bread, was an ideal component of a meal for a person with diabetes. The form in which it presented carbohydrate was mostly complex carbohydrate and this meant that less insulin would be needed than if the carbohydrate had been taken as glucose or sucrose.

**b) "The issue was not one of fast food necessarily being bad but a pizza ... was also very high in fat because of the cheese content"**

Lilly submitted that the pizza illustrated in the advertisement was a vegetarian pizza containing all of the elements of the "Mediterranean" diet which had been advocated by many as being healthy. Although pizza did contain cheese the amount was small in proportion to the whole and the fat content was therefore relatively small. Nutritional information from the packaging for a pizza similar to the one illustrated in the advertisement gave the fat content as 5.6g/100g of which 3.6g/100g were saturates; 1.6g were mono-unsaturates and 0.1g were polyunsaturates.

The fat content of other fast foods was much greater as could be seen from the labelling on supermarket packages. For example, ham and mushroom pizza 5.6g; haddock and chips 6.9g; chicken korma with pilau rice 9.3g; cheeseburger (without chips) 9.8g.

Of all of the types of fast food which could have been chosen to illustrate the advertisement, pizza was lowest in fat. Since the complaint was not about fast food *per se*, it followed that, if fast food was not a problem for the complainant, then pizza was less likely to be a problem in the complainant's eyes once the nutritional information about fast food was compared objectively.

Whilst the fat in pizza was visually apparent in the cheese topping, the hidden fat in other fast foods such as take away curries was far greater in absolute quantity.

**c) "Both of these facts were likely to result in an increase in weight which was not healthy for anyone and especially people with diabetes because of their susceptibility to long term complications such as heart disease"**

**Weight**

The control of weight in people with diabetes was a specific problem for people with type II diabetes for which diet was first line therapy. Only a minority of people with type II diabetes ever ended up on insulin and Humalog was unlikely to be the formulation of choice in these people.

Control of weight was not a problem for people with type I diabetes, indeed preventing loss of weight (one of the presenting symptoms) was part of the treatment. Insulin was the first line therapy for all people with type I diabetes. The importance of the minutiae of dietary control, which were crucial to the management of type II diabetes, were not so important in the management of type I diabetes now that a variety of insulins was available allowing the normalisation of post prandial glucose excursions (Gale and Tattersall (1990)). Thus people likely to receive Humalog were not at risk of being obese.

**Heart disease**

Although heart disease was a particular problem for people with type II diabetes it was not the most important problem in people with insulin dependent diabetes for whom renal, ophthalmological and neurological complications posed far more of a threat. This was because of the different underlying metabolic abnormalities (the problem in type II diabetes was more complex than pure insulin deficiency).

Thus the concerns about obesity and heart disease, whilst appropriate to type II diabetes, were not relevant to the people with type I diabetes likely to receive Humalog.

Since overweight and heart disease were not major problems in people with type I diabetes (the vast majority of people receiving insulin therapy) this point did not amount to a reasonable complaint against the advertisement. Indeed it should be remembered that all food must be viewed as part of a balanced diet, not just fast food.

**d) The underlying message was not in the interests of people with diabetes**

The best interests of people with diabetes varied depending upon the type of diabetes. Furthermore the social integration and acceptance of people with diabetes as being otherwise normal was hampered greatly by the imposition of strict dietary rules. From a holistic point of view it was therefore in the interests of people with diabetes to order their affairs so as to enable them to lead lives as normal to those of their non-diabetic fellow citizens. Fast food, much of which was inappropriate for people with diabetes to eat, was a major component of modern culinary culture. That pizza was the least inappropriate type of fast food available was an important piece of information for people with diabetes.

If the underlying message of the advertisement was that "with insulin lispro a more flexible and normal modern lifestyle is possible for people with diabetes (including eating pizza)" then this was surely a good message and one that was indeed in the interests of people with diabetes.

**e) The underlying message was not within the guidelines for healthy eating**

Lilly stated that it was hard to determine how general guidelines on healthy eating might be applied to an advertisement illustrating a pizza in the context of the treatment of diabetes. Nevertheless, as had been pointed out above, if fast food was not bad *per se* then pizza was much the healthiest of the options available.

The nutritional data on pizza and other fast foods was interesting given that it was at variance with the outward appearances of the products. In this context pizza, which displayed its fat content so obviously, was actually much lower in fat than other widely enjoyed fast foods.

Given that fast food was a fact of modern life, pizza was the closest approximation to healthy eating available within this broad category of food stuffs. It was therefore concluded that this aspect of the complaint was not supported by the available scientific evidence.

Lilly submitted that there had been no breach of the Code.

## PANEL RULING

The Panel did not accept that the underlying message of the advertisement was to promote unhealthy eating and hence encourage the use of Humalog. The Panel noted, however, that the pizza was not vegetarian as stated by the respondent, but appeared to have pepperoni on it.

The Humalog summary of product characteristics stated that its rapid onset of activity allowed Humalog to be given very close to mealtime. The bullet points at the bottom of the advertisement described Humalog as "An inject-and-eat insulin" which could "now be given before or after meals". The strapline at the bottom read "Bringing flexibility to life". In the opinion of the Panel the intention of the advertisement was to associate the properties of Humalog with the demands of a busy, modern lifestyle. The Panel considered that the use of the illustration of a pizza was not unreasonable. No breach of Clause 9.1 of the Code was ruled.

**Complaint received** 24 June 1998

**Case completed** 13 August 1998

---

**CASE AUTH/729/6/98** *NO BREACH OF THE CODE*

# FORMER HEALTH SERVICE MANAGER v MERCK SHARP & DOHME

## Zocor advertisement in Health Service Journal

**A former health service manager complained about an advertisement for Zocor issued by Merck Sharp & Dohme which had appeared in the Health Service Journal, alleging that it was in breach because it was an advertisement for a prescription only medicine and because the content of the advertisement was not appropriate for the audience.**

**The Panel noted that the journal was a specialist professional title and was not aimed at the general public. The key factor was to whom the publication was aimed rather than whether it could be purchased by the general public. The Panel did not accept that the advertisement was an advertisement to the public as alleged. The publication was an acceptable vehicle for advertisements for prescription only medicines and no breach was ruled in that regard.**

**Information from a readership survey showed that the journal was mainly read by administrative and general management personnel and by only a small number of clinicians. The publisher had stated in a previous case that the Health Service Journal was for the wide range of professionals who managed the provision of healthcare.**

**The advertisement referred to the recently published new findings of a study and the Panel noted the claims made for Zocor in the advertisement, "34% risk reduction in total mortality (p=0.009)" and "Proven to save the lives of elderly post-MI and angina patients". In the Panel's view the data presented in the advertisement was relevant to managers within the health service as it had implications for demands on it and the Panel therefore ruled no breach of the Code.**

A former health service manager complained about an advertisement which appeared in a supplement to the the Health Service Journal, 25 June 1998. An advertisement for Zocor (simvastatin), issued by Merck Sharp & Dohme Limited, detailed new data from the Scandinavian Simvastatin Survival Study and featured the claims "34% risk reduction in total mortality (p = 0.009)" and "Proven to save lives of elderly post-MI and angina patients".

## COMPLAINT

The complainant stated that bearing in mind Clauses 12.1 and 20.1, the noise that could be heard was a coach and horses being driven through the Code. The complainant considered that because of the Authority's arcane rules he could do nothing informally, only complain formally, which he did now.

The complainant stated that the journal knew the Code as well as anyone else, and so did pharmaceutical companies. The complainant wanted it clearly known that he wanted greater openness for patients and managers but as the rules stood this type of advertising was not permitted.

## RESPONSE

Merck Sharp & Dohme stated that the Health Service Journal was targeted toward health service management and not towards the general public. It was the likely audience for a journal which was relevant as to whether advertising of prescription only medicines was allowable within the journal, and not the fact that the public could buy it. Clearly the general public had easy access to the British Medical Journal and The Lancet but advertisements for prescription only medicines were allowable as the intended audience was professional.

Merck Sharp & Dohme stated that if the contention of the complainant was that the audience within the NHS constituted 'general public' and not a professional audience then the company rejected this also. The reader profile survey for the journal indicated clearly that the majority of readers were professional managers (a copy of the survey was provided). Professional managers within the NHS were frequently involved in decisions which impacted on prescribing and were required to be knowledgeable in complex disease areas, as reflected in a variety of articles within the journal (a copy of the journal was provided). As such, professional NHS managers, fell within the definition of 'appropriate administrative staff' mentioned in Clause 1.1.

Merck and Sharp & Dohme rejected the allegation that the Zocor advertisement used was inappropriate for the audience to whom it was directed. The company noted that the advertisement was within a 'pull-out' section of the journal entitled 'Managers and Medicine'. Within this

section complex medical issues were discussed including paediatric surgery, osteoporosis and its management, cardiac surgery and multiple sclerosis. These subjects were not treated superficially but included explanations of such disparate things as pyloric stenosis, intersusseption, bisphosphonate use, percutaneous transluminal coronary angioplasty and a breakdown of the four types of multiple sclerosis.

Clearly this journal had a knowledgeable audience which was capable of understanding the concept of the '34% risk reduction in total mortality' featured in the advertisement. Indeed the opening article in 'Managers and Medicine' discussed cancer mortality and issues around reducing it by 20% in the under 65s, and an article on heart bypass operations discussed the relative merits of procedures by referring to a meta-analysis comparing mortality rates and other endpoints.

Merck Sharp & Dohme stated that given that the audience understood the advertisement, the question might be raised as to whether it was a valid point to make to this audience. The company would assert that it was and noted the importance given to mortality figures elsewhere in this journal which illustrated the value this readership placed on evidence based medicine and hard endpoints.

Merck Sharp and Dohme rejected the complaints and the terms in which they were made. The company rejected utterly the implication in the complaint (by use of the "coach and horses" analogy) that it would at any time flout the Code in a deliberate and calculated fashion.

With regard to Clause 20.1 the company considered that it was entirely appropriate to advertise in the Health Service Journal which by its content and readership was demonstrably directed towards professional health service management. The company contended that health service management was clearly 'appropriate administrative staff' as mentioned in Clause 1.1 of the Code.

With regard to Clause 12.1 the terms used in the advertisement were entirely in keeping with the rest of the journal and the knowledge base of its intended audience. The advertisement illustrated a point which was likely to be of interest and value to an audience whose decisions impacted on prescribing.

## PANEL RULING

The Panel noted that Clause 1.1 of the Code stated that the Code applied to the promotion of medicines to members of the UK health professions and to appropriate administrative staff. The relevant supplementary information referred to Clause 12.1 which required that promotional material should only be sent or distributed to those persons whose need for, or interest in it, could reasonably be assumed. The supplementary information to Clause 12.1 stated that promotional material should be tailored to the audience to whom it was directed.

The Panel noted that there had been previous cases concerning advertisements for prescription only medicines in a publication for healthcare workers. In Case AUTH/145/4/94 no breach of the Code had been ruled. The Panel had considered that the advertisement was not an advertisement to the public as alleged and that the publication was an acceptable vehicle for advertisements of prescription only medicines. Another more recent case, Case AUTH/720/6/98, concerned an advertisement in the Health Service Journal. The Panel had considered that the advertisement was not an advertisement to the public and that the journal was an acceptable vehicle for advertisements of prescription only medicines. The Panel had ruled a breach of Clause 12.1 of the Code as the wording of the advertisement had not been tailored to the audience.

The Panel examined the materials now before it. The Health Service Journal was a specialist professional title and was not aimed at the general public. The Panel considered that the key factor was to whom the publication was aimed rather than whether it could be purchased by the general public. The Panel did not accept that the advertisement was an advertisement to the public as alleged and considered that the publication was an acceptable vehicle for advertisements of prescription only medicines. The Panel therefore ruled no breach of Clause 20.1 of the Code.

The Panel then considered whether the content of the advertisement was suitable for the readership of the journal. The information from the readership survey showed that the journal was mainly read by administrative and general management personnel and by only a small number of clinicians. The publisher had stated in a previous case, Case AUTH/720/6/98, that the Health Service Journal was for the wide range of professionals who managed the provision of healthcare.

The Panel noted that the advertisement referred to the recently published new findings of a study. The Panel noted the claims made for Zocor in the advertisement, "34% risk reduction in total mortality (p=0.009)" and "Proven to save the lives of elderly post-MI and angina patients". In the Panel's view the data presented in the advertisement was relevant to managers within the health service as it had implications for demands on the health service. The Panel therefore ruled no breach of Clause 12.1 of the Code.

**Complaint received** **25 June 1998**

**Case completed** **12 August 1998**

CASE AUTH/730/6/98

# FORMER HEALTH SERVICE MANAGER v HOECHST MARION ROUSSEL

## Telfast 120 advertisement in Health Service Journal

**A former health service manager complained about an advertisement for Telfast 120 issued by Hoechst Marion Roussel which had appeared in a supplement to the Health Service Journal, alleging that it was in breach because it was an advertisement for a prescription only medicine to the public and because the content of the advertisement was not appropriate for the audience.**

**The Panel noted that the journal was a specialist title and was not aimed at the general public. The key factor was to whom a publication was aimed rather than whether it could be purchased by the general public. The Panel did not accept that the advertisement was an advertisement to the public as alleged. The journal was an acceptable vehicle for advertisements for prescription only medicines and no breach was ruled in that regard.**

**The Panel noted that the only information given in the advertisement was that it was for the treatment of allergies, in particular hay fever. There was no information which could be used for a management decision. The Panel did not consider that the information had been tailored to the audience to which it was directed and a breach was ruled.**

A former health service manager complained about an advertisement which had appeared in a supplement to the Health Service Journal, 25 June 1998. The advertisement was for Telfast 120 and had been issued by Hoechst Marion Roussel Limited. It featured an aerial photograph of a young woman and a sunflower and was headed "Hayfever-free zone". The strapline, along the bottom of the advertisement, was "When allergies control lives, control allergies with Telfast". The only other copy was the prescribing information and the company name.

### COMPLAINT

The complainant stated that bearing in mind Clauses 12.1 and 20.1, the noise that could be heard was of a coach and horses being driven through the Code. The complainant considered that because of the Authority's arcane rules he could do nothing informally, only complain formally, which he did now.

The complainant stated that the journal knew the Code as well as anyone else, and so did pharmaceutical companies. The complainant wanted it clearly known that he wanted greater openness for patients and managers but as the rules stood this type of advertising was not permitted.

### RESPONSE

Hoechst Marion Roussel stated that it understood the Health Service Journal to be a professional publication with a specialised readership aimed at personnel with responsibility for managing the provision of healthcare and who made decisions which impacted on the purchase of medicines. The company further understood that the major part of the circulation of the journal was by subscription, with a relatively minor number of copies being purchased on news-stands or in news agencies. It could not be considered as being read by or sold to the general public, any more than other specialised medical publications such as the British Medical Journal or The Lancet. The company therefore considered it entirely appropriate to advertise its products to the readers of the Health Service Journal on the basis that they were often responsible for controlling spending within practices, trust directorates and other such settings. Hoechst Marion Roussel considered that readers would therefore have an interest in information on products that fulfilled a clear clinical need and, within their therapeutic category, were advantageously priced.

Hoechst Marion Roussel noted that the edition of the journal in which its advertisement appeared carried promotional material for other prescription-only medicines, implying its understanding of the journal's intended audience was shared by other companies.

Hoechst Marion Roussel stated that it was fully aware of the obligations placed upon it by Clause 20 and indeed by the relevant legislation and it had never been the company's intention to flout either. However, the Code permitted promotion of medicines to appropriate administrative staff, as was clear from the supplementary information to Clause 1.1. It was in this context that the advertisement in the Health Service Journal was placed. As outlined above the company did not consider that this journal was directed to members of the general public. Hoechst Marion Roussel noted a previous ruling on a similar matter (Case AUTH/145/4/94), in which it was determined that the important factor was to whom the publication was aimed and not whether or not it might be purchased by the general public.

Hoechst Marion Roussel provided a copy of a letter from the publishers of the Health Service Journal which described the readership of the journal and included a readership survey.

Hoechst Marion Roussel denied any breach of Clauses 12.1 or 20.1 of the Code.

### PANEL RULING

The Panel noted that Clause 1.1 of the Code stated that the Code applied to the promotion of medicines to members of the UK health professions and to appropriate administrative staff. The relevant supplementary information referred to Clause 12.1 which required that promotional material should only be sent or distributed to those persons whose need for, or interest in it, could reasonably be assumed. The supplementary information to Clause 12.1 stated that promotional material should be tailored to the audience to whom it was directed.

The Panel noted that there had been previous cases concerning advertisements for prescription only medicines in a publication for healthcare workers. In Case AUTH/145/4/94 the Panel had considered that the advertisement was not an advertisement to the public as alleged and that the publication was an acceptable vehicle for advertisements of prescription only medicines. Another more recent case, Case AUTH/720/6/98, concerned an advertisement in the Health Service Journal. The Panel had considered that the advertisement was not an advertisement to the public and that the journal was an acceptable vehicle for advertisements of prescription only medicines. The Panel had ruled a breach of Clause 12.1 of the Code as the wording of the advertisement had not been tailored to the audience.

The Panel examined the materials now before it. The Health Service Journal was a specialist professional title and was not aimed at the general public. The Panel considered that the key factor was to whom the publication was aimed rather than whether it could be purchased by the general public. The Panel did not accept that the advertisement was an advertisement to the public as alleged and considered that the publication was an acceptable vehicle for advertisements for prescription only medicines. The Panel therefore ruled no breach of Clause 20.1 of the Code.

The Panel then considered whether the content of the advertisement was suitable for the readership of the journal. The information from the readership survey showed that the journal was mainly read by administrative and general management personnel and by only a small number of clinicians. The publisher stated that the Health Service Journal was for the wide range of professionals who managed the provision of healthcare.

The Panel noted that the only information given in the Telfast 120 advertisement was that the product was for the treatment of allergies, in particular hayfever. There was no information included which could be used to make a management decision about Telfast. The Panel noted Hoechst Marion Roussel's submission that readers of the Health Service Journal would have an interest in products which fulfilled a clinical need and which, within their therapeutic category, were competitively priced. The only information regarding the cost of Telfast was that given in the prescribing information. No information was given about the cost of other products. The Panel did not consider that the advertisement had been tailored to the audience to which it was directed. A breach of Clause 12.1 of the Code was ruled.

**Complaint received** **25 June 1998**

**Case completed** **7 August 1998**

---

**CASE AUTH/731/6/98**

# DERMAL v GOLDSHIELD

## Promotion of Fenbid

**Dermal complained about a mailing and a "Dear Doctor" letter for Fenbid Gel issued by Goldshield. A price comparison chart in the mailing was ruled in breach as it used the brand names of other companies' products without consent. Further breaches were ruled because the Panel considered that the price comparison chart was visually misleading. Each column started with the price of Fenbid. There appeared to be no logical reason to support the order of the products in the columns. There were inconsistencies in the data in each column. A further breach was ruled because of the absence of prescribing information for Fenbid.**

**A claim in the "Dear Doctor" letter "... Fenbid Gel is the most cost effective of all branded topical NSAID's" was considered to be misleading and ruled in breach. In the Panel's view, "cost effective" implied more than a simple comparison of the costs of the products. Other factors such as relative efficacy, indications and incidence of side-effects had to be taken into account.**

Dermal Laboratories Limited complained about a mailing (ref GG028M08) and a "Dear Doctor" letter (ref LGG03) for Fenbid Gel (ibuprofen 5% w/w) issued by Goldshield Pharmaceuticals.

### 1 Price comparison chart

The mailing was a single A4 sheet and featured, on one side, a cost comparison chart which by use of three equal length columns of data compared the cost of 30g, 50g or 100g of a number of topical non-steroidal anti-inflammatory drugs (NSAIDs). Each column started with the cost of Fenbid, ie £2.10, £2.65 and £5.25 for the 30g, 50g and 100g tube respectively. The costs of other topical NSAIDs were given up the column with each product being identified by brand name. The reverse of the mailing featured more claims for Fenbid and a coupon to obtain a free sample pack of four 30g tubes of the gel.

### COMPLAINT

Dermal stated that blatant use had been made of other companies' brand names (eg Dermal's Ibugel) in breach of Clause 7.10 of the Code. In addition the price comparison chart had a suppressed zero, inconsistent scale, and omitted several low cost topical NSAIDs (Cuprofen, Ibuprofen Gel, Ralgex, Powergel). Dermal alleged a breach of Clause 7.6 of the Code. Dermal also noted that the price comparison chart was a stand-alone item yet did not contain the requisite prescribing information in breach of Clause 4.1 of the Code.

### RESPONSE

Goldshield apologised for the use of other companies' brand names and stated that it would ensure that it did not happen again. With regard to Clause 7.6 and 4.1 of the Code the company would endeavour to ensure that all price comparison charts were accurate in future, and did not include any scales that provided a misleading claim.

## PANEL RULING

The Panel noted that Clause 7.10 of the Code stated that the brand names of other companies' products must not be used unless prior consent of the proprietors had been obtained. The Panel noted that the topical NSAIDs in the price comparison chart had been identified by brand name alone. Dermal had not granted permission for its brand name Ibugel to be used. The Panel therefore ruled a breach of Clause 7.10 of the Code.

The Panel noted that each column of data started with the cost of Fenbid. The Panel considered that this was misleading as Fenbid was thus shown as the cheapest option. This might not always be the case for example a 100g tube of Movelat cost less than a 100g tube of Fenbid.

The Panel examined the data in each column. The 30g column started with the cost of Fenbid, £2.10. The next cost shown was Ibuleve at £2.42 followed by Proflex at £2.29. The spacing between Ibuleve and Proflex create the impression that Proflex was significantly more expensive than Ibuleve. There appeared to be no logical reason to support the order of the products in each column. The Panel noted that Proflex was not available in a 30g tube (ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1998-99). Visually, the most expensive NSAID in the 30g column was Traxam although the cost was given as only £2.10. Again the Panel noted that Traxam was not available in a 30g tube. The cost stated for Traxam appeared to be based on the cost of the 100g tube but in the Panel's view to state a pro rata cost when the whole 100g had to be purchased was misleading. Similar inconsistencies were noted in the other two columns.

Overall the Panel considered that visually the price comparison chart was misleading and the data contained therein inaccurate. Breaches of Clauses 7.6 and 7.2 of the Code were ruled.

The Panel noted that the mailing which featured the price comparison chart did not include the prescribing information for Fenbid. Although it appeared to the Panel that the mailing had been sent with a "Dear Doctor" letter (ref LGG03), which did have the prescribing information on the reverse, each item had to stand alone. Prescribing information must form part of the promotional material and must not be separate from it. The Panel accordingly ruled a breach of Clause 4.1 of the Code.

### 2 Claim ".... Fenbid Gel is the most cost-effective of all branded topical NSAIDs."

This claim appeared on a "Dear Doctor" letter (ref LGG06).

## COMPLAINT

Dermal stated that there was no basis for this claim. Fenbid Gel might be cheap, assessed simply on a cost-per-gram basis, but this took no account of different dosage recommendations, different indications (eg Ibugel was indicated for arthritic pain, whereas Fenbid was not), or even different medicines. Dermal alleged a breach of Clause 7.2.

## RESPONSE

Goldshield did not accept that this claim had breached the Code. Fenbid Gel was indicated for non-serious arthritic conditions which could be seen from the summary of product characteristics.

## PANEL RULING

The Panel noted that the "Dear Doctor" letter was headed "New evidence of topical NSAID effectiveness" and detailed some positive results for topical ibuprofen taken from a recently published meta-analysis of topical NSAID trials. The claim in question was made in a paragraph of the letter which read "Unbeatable cost-effectiveness among topical NSAID brands. At between £2.10 (30g tube) and £5.25 (100g tube), Fenbid Gel is the most cost effective of all branded topical NSAIDs ...".

The Panel noted that the supplementary information to Clause 7.2 of the Code stated that care must be taken that any claim involving an economic evaluation of a medicine was borne out by the data and did not exaggerate its significance. In the Panel's view "cost-effective" implied more than just a simple comparison of the costs of the products. Other factors such as relative efficacy, incidence of side effects etc had to be taken into account. The Panel noted that Fenbid Gel was indicated for non-serious arthritic conditions. Some topical NSAIDs, for example piroxicam gel, were indicated for the treatment of osteoarthritis of superficial joints. The Panel noted that no account of the differing indications for topical NSAIDs had been made in the claim in question.

Overall the Panel considered that the claim "Fenbid Gel is the most cost effective of all branded topical NSAIDs" was misleading and ruled a breach of Clause 7.2 of the Code.

**Complaint received** **26 June 1998**

**Case completed** **7 September 1998**

CASE AUTH/732/6/98

# DIRECTOR/PARAGRAPH 16 v SCHERING-PLOUGH

## Sponsorship of a medical dinner dance

**This case arose from the Panel's consideration of a previous case, AUTH/709/5/98, which concerned a complaint about a Clarityn leavepiece distributed by Schering-Plough. The leavepiece had been distributed at a dinner dance. The matter was taken up under the provisions of Paragraph 16 of the Constitution and Procedure.**

**Schering-Plough had paid £500 for exhibition space at the meeting which was for general practitioners and hospital staff. The exhibition had been held in a separate room. A formal medical lecture had been given by the guest speaker.**

**The Panel did not consider that the event, which was referred to as a medical dinner dance, had an educational content such as to justify support. In the Panel's view the main purpose of the evening was a social event and it was unacceptable for Schering-Plough to sponsor the exhibition. A breach of the Code was ruled.**

### COMPLAINT

This case arose from the Panel's consideration of Case AUTH/709/5/98 which concerned a complaint from UCB Pharma Limited that Schering-Plough Ltd was continuing to distribute a leavepiece for Clarityn which had been ruled in breach of the Code. The leavepiece had been distributed at a dinner dance. The Panel considered that there was a possible breach of Clause 19 in relation to Schering-Plough's involvement with the dinner dance and decided that the matter should be taken up with Schering-Plough under the provisions of Paragraph 16 of the Constitution and Procedure.

### RESPONSE

Schering-Plough stated that a meeting for general practitioners and hospital doctors had taken place on Friday, 8 May 1998 at a named hotel. The meeting had been organised by a general practitioner and its primary purpose was medical education. The company understood that spouses of the general practitioners and hospital medical staff were invited to the meeting for which they bore the cost. Schering-Plough was not involved and did not fund the attendance of any spouses at the meeting. Schering-Plough stated that a fee of £500, to exhibit, was paid to the organising committee. The fee was explicitly to purchase exhibition space at the meeting and for no other purpose. Three representatives from the company had attended the meeting, arriving at 6:15pm, putting up the exhibition stand before the commencement of the exhibition at 7pm. The exhibition had taken place in a separate room to the dinner and the presentation. Eleven other pharmaceutical companies had exhibited at the meeting. Doctors attending the meeting had been encouraged to visit the exhibition prior to dinner at 8pm. To the best of the company's knowledge, the exhibition area had only been visited by members of the medical profession.

Schering Plough stated that a formal medical lecture had been given by the guest speaker, an emeritus consultant anaesthetist, entitled "Dealing with difficult patients", which had lasted one hour. One of the organisers had also spoken at the meeting, but his presentation was short and by way of introduction to the guest speaker.

Schering-Plough submitted that the primary purpose of the meeting had been educational and that the company's presence and fee paid for exhibition space at this meeting had not been in breach of Clause 19 of the Code.

* * *

The general practitioner who organised the event wrote independently to the Authority about the annual medical dinner stating that it adhered to ABPI guidelines. Eminent medical personnel addressed the doctors to update them with current medical trends. Non-medical spouses had to pay £10 per head. The medical exhibition was sponsored by reputable companies and was visited by only the medical personnel. A copy of the invitation was provided.

The invitation was to the a medical dinner dance and stated that, to comply with ABPI regulations, a charge of £10 was payable for non-medical spouses. The invitation did not give the time of the dinner but stated that there would be a sherry reception at 7:30pm. The invitation gave details of the guest speaker.

### PANEL RULING

The Panel accepted that fees for exhibition stands often subsidised the overall cost of a conference or a meeting etc. The amount paid had, however, to be reasonable for the exhibition facilities which were provided. Exhibition fees could not knowingly be used as a means of hidden subsidy for unacceptable activities. The overall arrangements for a meeting associated with an exhibition would have to comply with the requirements of Clause 19 of the Code. The meeting must have a clear educational content, any hospitality provided by a pharmaceutical company must be appropriate and not out of proportion to the occasion. Hospitality must not be extended to spouses and others unless they qualified as delegates in their own right. Further, all materials had to comply with the Code and the exhibition should not be open to members of the public if promotional material for prescription only medicines was to be displayed.

In the case now before it, the Panel did not consider that the medical dinner dance in question had an educational content such as to justify support. Although there was a speaker talking about how to deal with difficult patients the speech was given to a mixed audience and in the Panel's view would have been more of an after dinner speech than an educational presentation. The Panel noted Schering-Plough's submission that the primary purpose of the meeting was educational but did not accept that, within the context of a dinner dance, the speech could be regarded as a formal medical lecture. The main purpose of the evening was a social event.

In the view of the Panel, any form of support for such an event which was almost wholly social in nature, whether by direct sponsorship or by sponsorship through the taking of an exhibition stand, was unacceptable in relation to the requirements of the Code.

The Panel therefore ruled a breach of Clause 19.1 of the Code.

The Panel noted that non-medical guests had had to pay £10 in order "to comply with ABPI regulations" and questioned whether this was so. It queried whether £10 represented the true cost of attending the dinner dance.

**Proceedings commenced** **12 June 1998**

**Case completed** **13 July 1998**

---

**CASE AUTH/733/6/98**

# CONSULTANT HAEMATOLOGIST v WYETH

## Zoton advertisements

**A consultant haematologist complained about three journal advertisements for Zoton issued by Wyeth which depicted respectively a polar explorer, a water skiing champion and an Anglican priest, all of whom were doctors. Beneath each photograph was a highlighted caption box containing the name of the doctor, details of their non-medical activity and the phrase "No ordinary doctor". Each advertisement carried a disclaimer that the appearance of the doctor did not imply his or her endorsement of Zoton. The complainant considered that the doctors would inevitably be seen as endorsing the product and the disclaimer did not remove this impression. The advertisements were irresponsible and unethical. Health professionals were not supposed to endorse medicines.**

**The Panel noted that a further similar advertisement which featured an eminent doctor who was also a portrait painter had been ruled in breach by the Appeal Board following an earlier complaint from the same complainant (Case AUTH/662/1/98). The Appeal Board had considered that readers would assume his appearance was an endorsement of the product and it was not customary practice for photographs of health professionals to be used in advertising. Although the doctors featured in the three advertisements now before it were not as well known as the doctor in the previous one, the Panel considered that the same principle applied and each advertisement was ruled to be in breach.**

A consultant haematologist complained about three in a series of four advertisements for Zoton which depicted a polar explorer, a water skiing champion and an Anglican priest. The fourth advertisement in the series depicted a portrait painter. The individuals in the advertisements were all named medical practitioners. The fourth advertisement had been the subject of an earlier complaint from the same complainant, Case AUTH/662/1/98.

### COMPLAINT

The complainant stated that all of the advertisements were designed to create the impression that a medical practitioner endorsed Zoton. They were thus irresponsible and unethical.

The medical practitioners' involvement in the advertisements was contrary to the conventions of their profession and as such violated Clause 9.2 of the Code. The doctors should have realised that, rightly or wrongly, many readers would assume that their appearance represented an implicit endorsement and that it was motivated by financial gain. For the Panel to conclude that any of the three advertisements complied with the Code would set an appalling precedent and would open the gates to massive abuse of a similar kind in the future. Where would such 'endorsement by the back door' stop?

The complainant noted Wyeth's admission in Case AUTH/662/1/98 that "the focus [of the four advertisements] was not the doctors' professional reputation ... but what they had achieved outside the field of medicine". The fact, therefore, that the medical practitioner in the fourth advertisement was more eminent than the other doctors should have no bearing whatsoever on the Panel's decision.

The complainant stated that all of the principles upheld by the Panel and the Appeal Board with respect to Case AUTH/662/1/98 were equally applicable to the other advertisements in the set. Specifically:

- Health professionals were not supposed to endorse medical products.
- The doctors would inevitably be seen as endorsing the product, and the inclusion of a disclaimer did not remove this impression.
- It was a principle of the Code that misleading impressions could not be corrected by footnotes or disclaimers.

The complainant stated that it was well known that the medical practitioner in the fourth advertisement worked in a branch of medicine in which Zoton was seldom used. The vast majority of readers, however, would not know in which branch of medicine the other doctors worked, and thus the potential for them to interpret the practitioners' involvement as an implicit endorsement was very much greater.

In the complainant's view the Panel had an opportunity to send a clear message to the pharmaceutical industry that under no circumstances must medical practitioners be used in advertisements for medical products. The complainant urged it to use the opportunity wisely.

### RESPONSE

Wyeth stated that having been advised by the Authority that the Appeal Board's ruling in Case AUTH/662/1/98 applied only to that advertisement, it quite understood that the only mechanism for establishing the status of the

remaining three advertisements with certainty was to have them formally adjudicated upon as a separate complaint. Wyeth welcomed this opportunity for clarification.

Wyeth submitted that the focus of the three advertisements was not the doctors' professional reputations or status, but what they had achieved outside the field of medicine. These advertisements should be distinguished from the fourth advertisement in that the three doctors concerned, while no doubt excellent doctors, were not generally regarded as pre-eminent in their professional fields.

The doctors were not presented as endorsing the product in that a disclaimer was included in the advertisements. The typesize of this disclaimer had now been increased so that there could be no doubt about its legibility and prominence. The wording of the disclaimers was dictated by the doctors' respective medical defence organisations.

Having regard to above, the appearance of the doctors in the advertisement was not contrary to the conventions of the medical profession and did not therefore breach Clause 9.2.

### PANEL RULING

The Panel examined the advertisements in question. The main feature of each advertisement was a striking colour photograph of the individual concerned in their non-medical role as either a polar explorer, water skiing champion or Anglican priest. Beneath the photograph was a highlighted caption box containing the name of the medical practitioner, details of their non-medical activity followed by the phrase "No ordinary doctor". Each advertisement carried a disclaimer to the effect that the appearance of the doctor did not imply his or her endorsement of Zoton. In the Panel's view, however, this did not remove the clear impression that the doctors did endorse the product.

The Panel noted that the fourth advertisement in the series, which featured an eminent professor in his role as a portrait painter, had been the subject of a separate complaint, Case AUTH/662/1/98. In that case the Appeal Board had ruled that readers would assume that his appearance in the advertisement was an endorsement of the product and that it was not customary practice for photographs of health professionals to be used in advertising. A breach of Clause 9.2 of the Code had been ruled.

The Panel considered that the ruling in Case AUTH/662/1/98 applied to the case now before it. It was not customary practice for health professionals to appear in pharmaceutical advertising. Whilst the Panel accepted that the medical practitioners featured were not as well known within the medical profession as the professor featured in the fourth advertisement, their appearance in the advertisements was nonetheless an endorsement of the product. The Panel ruled that each advertisement was in breach of Clause 9.2 of the Code.

**Complaint received** **30 June 1998**

**Case completed** **7 September 1998**

---

**CASE AUTH/734/6/98** *NO BREACH OF THE CODE*

# DIRECTOR/MEDIA v ROCHE

## Promotion of Posicor

**A commentary in The Lancet was critical of the promotion of Posicor (mibefradil) by Roche. The product had been withdrawn but the Authority was nonetheless obliged to take up the matter as a complaint. The authors stated that there was little modesty in the promotion of the product which was claimed to be a first line therapeutic agent for hypertension and angina. Given the absence of long term studies objective observers would classify it as a second line agent that deserved a black triangle to indicate limited experience.**

**The Panel noted that the indications for Posicor in its SPC were "... the treatment of essential hypertension" and "... the treatment of stable angina pectoris". There was no statement to suggest that Posicor could only be given as a second line medicine, for example in patients who were resistant to, or intolerant of, other medicines. The Panel considered, therefore, that within the terms of its SPC Posicor could be given to newly diagnosed hypertensive or angina patients. The Panel noted that promotional material for Posicor referred to the product as "A new first line therapy in hypertension and angina". The Panel considered that the SPC did not prohibit its use as a first line agent. The Posicor advertisements were not inconsistent with the indications in the SPC and the Panel ruled no breach of the Code.**

**The Panel noted that the Posicor SPC and the promotional material that had been provided included an inverted black triangle to denote that special reporting was required in relation to adverse reactions. This was not a Code or a statutory requirement. All new clinical entities were required to include a black triangle as a result of an agreement between the Committee on Safety of Medicines and the ABPI.**

A commentary in The Lancet, June 20 1998, discussed the recent withdrawal by Roche Products Limited of Posicor (mibefradil). The Lancet commentary was critical of advertisements for the product. The product had been withdrawn but the Authority was nonetheless obliged in accordance with established procedure, to deal with the matter as a complaint under the Code.

### COMPLAINT

The authors of the commentary stated that advertisements for mibefradil suggested that there was little modesty in the promotion of the medicine, which was claimed to be a first line therapeutic agent for hypertension and angina. Given the absence of long-term studies such as those that had established thiazide diuretics and ß-blockers as truly first line therapy for hypertension, objective observers would classify mibefradil as a second line agent that

deserved a blank triangle (to indicate limited experience) in the British National Formulary. The authors questioned how the industry's advertising authority had allowed this claim to pass through.

## RESPONSE

Roche submitted that the summary of product characteristics (SPC) for Posicor, like all other new antihypertensive agents, was based on a mixture of clinical trials, both in the setting where Posicor had been investigated as monotherapy and in addition to other treatments (eg thiazide diuretics). The therapeutic indications were drawn from this data and stated, simply and clearly "treatment of essential hypertension" and "treatment of stable angina pectoris". There was no limitation or stipulation as to "first line" or "second line" usage in the licensed indications. Given these approved indications and the fact that most of the clinical data on efficacy and tolerability was based upon first line use of Posicor, the company considered that its advertising was in line with the SPC and Clauses 3.2 and 7.2 of the Code. In addition, the advertising had not used superlatives and in particular, Roche had been very careful not to state or imply that Posicor was the "only" or the "best" potential first line therapeutic agent. The company considered, therefore, that it had also complied with Clause 7.8 of the Code.

Roche provided photocopies of a number of promotional pieces for Posicor.

## PANEL RULING

The Panel noted that the authors of the commentary had been advised that the Authority did not pre-approve advertisements to health professionals. The requirements for certification had also been pointed out.

The Panel noted that the indications for Posicor in the SPC were "... the treatment of essential hypertension" and "... the treatment of stable angina pectoris". There was no statement in the SPC to suggest that Posicor could only be given as a second line medicine, for example in patients who were resistant to, or intolerant of, other medicines. The Panel considered, therefore, that within the terms of its SPC Posicor could be given to newly diagnosed hypertensive or angina patients.

The Panel noted that promotional material for Posicor referred to the product as "A new first line therapy in hypertension and angina". The Panel considered that the SPC did not prohibit its use as a first line agent. The Panel considered that the Posicor advertisements were not inconsistent with the indications in the SPC and ruled no breach of the Code.

During its consideration of this case the Panel noted that the Posicor SPC and the promotional material that had been provided included an inverted black triangle to denote that special reporting was required in relation to adverse reactions. This was not a Code or a statutory requirement but was referred to in Clause 4.2 of the Code. All new chemical entities were required to include a black triangle. The use of the black triangle was the result of an agreement between the Committee on Safety of Medicines and the ABPI.

**Complaint received** **1 July 1998**

**Case completed** **19 August 1998**

CASES AUTH/735/7/98 and AUTH/736/7/98

# MERCK SHARP & DOHME v PARKE DAVIS AND PFIZER

## Promotion of Lipitor

**Merck Sharp & Dohme complained about the promotion of Lipitor (atorvastatin) by Parke Davis and Pfizer. The materials at issue were a leavepiece and a mailing, both of which were designed to give details of the CURVES study which aimed to evaluate the comparative dose efficacy of Lipitor with other statins.**

**Merck Sharp & Dohme alleged that the claim "Lipitor produced significant reductions in triglycerides", which was referenced to the CURVES study, would lead readers to conclude that the significant reductions were over and above the other statins which was not so. The significant reductions quoted were over baseline.**

**The Panel considered that the context of the claim and the impression from the material were important factors. The Panel considered that the claim was misleading in both the leavepiece and the mailing as it appeared beneath two comparative claims and a heading relating to the CURVES study. The impression given was that the claim related to a comparison of Lipitor with the other statins and not with baseline. A breach of the Code was ruled.**

**Upon appeal by Parke Davis and Pfizer the Appeal Board noted that the first piece of information given to readers in the leavepiece and mailing was the aim of the CURVES study and considered that the leavepiece and the mailing would be read in the light of this. The Appeal Board considered that most readers would view the claim in question as a comparative claim versus the other statins which was not so. The Appeal Board considered that, given the context within which it was written, the claim was misleading and upheld the Panel's ruling of a breach of the Code.**

**The claim "Lowers triglycerides by up to 45%" appeared as a bullet point on the back page of the leavepiece and the mailing and was alleged by Merck Sharp & Dohme to be exaggerated and misleading. The claim was based on a particular sub-group of patients taking 80mg Lipitor per day and ignored a larger body of evidence which showed that the maximum reduction in triglycerides levels was in the order of 30-33%. Merck Sharp & Dohme did not accept that "up to" negated the misleading impression; the percentage given must reflect what could generally be expected to be achieved with therapy.**

**The Panel noted that the claim was based on a small study the results for which were inconsistent with the information given in the summary of product characteristics and other data. The Panel considered that the claim was not a balanced reflection of all the available evidence. A breach of the Code was ruled.**

**Upon appeal by Parke Davis and Pfizer the Appeal Board noted that the claim appeared amongst a list of general claims for Lipitor. Lipitor had a range of doses from 10mg to 80mg daily. The claim preceding the claim in question stated that the majority of patients would reach their LDL-cholesterol lowering goals on 10mg daily. In the Appeal Board's view most patients would be treated with 10mg Lipitor daily. The Appeal Board considered that, with no indication to the contrary, the claim in question would also be assumed to relate to the 10mg daily dose which was not so. The Appeal Board considered that the claim would mislead readers as to the degree that triglyceride levels might be lowered using the starting dose of Lipitor. The Panel's ruling of a breach of the Code was upheld.**

Merck Sharp & Dohme Limited complained about the promotion of Lipitor (atorvastatin) by Parke Davis and Co Limited and Pfizer Limited.

The materials at issue were a leavepiece (ref: A670/90332) and a mailing sent to healthcare professionals (ref: Z963/90129B). Each piece gave details of the results from the CURVES study. The objective of the CURVES study was to evaluate the comparative dose efficacy of atorvastatin (Lipitor) with pravastatin, simvastatin, lovastatin and fluvastatin.

Pfizer requested that the response from Parke Davis was treated as the response on behalf of Pfizer. There were two allegations which were considered as follows:

### 1 Claim "Lipitor produced significant reductions in triglycerides"

The claim appeared as a bullet point in both the leavepiece and the mailing. The inside pages of the leavepiece formed a double page spread with the left hand page headed "The CURVES Study". Under the heading were details of the aim of the study, its design and a graph depicting mean % reduction in LDL-cholesterol from baseline for Lipitor, simvastatin, pravastatin and fluvastatin. The right hand page had three claims presented in bullet point style. The first two claims were for advantages of Lipitor compared with the other statins. The third bullet point was the claim in question. All of the claims were referenced to the CURVES study.

The mailing was laid out differently. One page of the mailing was headed "The CURVES Study: results" and included the same graph and three bullet points as in the leavepiece (the aim of the study and its design had been described on another page). Two of the bullet points were referenced to the CURVES study as in the mailing but there was no reference given to the claim in question.

#### COMPLAINT

Merck Sharp & Dohme alleged that because the claim was made adjacent to a graph comparing the potency of statins at lowering LDL-cholesterol, and in a leavepiece which was describing a study comparing statins, it would lead a reader to conclude that atorvastatin (Lipitor) produced significant reductions over and above the other statins whereas this was not so. The significant reduction quoted was over baseline triglyceride levels. Merck Sharp & Dohme alleged that the claim was in effect a hanging comparison in this situation as it was not clear what the significant reduction was in relation to. A breach of Clause 7.2 of the Code was alleged.

## RESPONSE

Parke Davis stated that the claim was supported by the summary of product characteristics (SPC) for Lipitor. It did not involve a comparator and so the concerns with respect to the comparative efficacy of other statins in the CURVES study had no relevance to this claim. The CURVES study showed that Lipitor produced significant reductions in triglyceride levels compared to baseline at each of its licensed dosages. Lipitor had a marketing authorization to lower triglycerides in patients with dyslipidaemia reflecting the fact that the company had demonstrated this, relative to baseline, to the regulatory authority's satisfaction. The use of the word "significant" in the claim was true both in the grammatical and the statistical sense. Clinicians would understand the company's intended meaning and it was very distinct from the other two preceding comparative claims which described the other products involved.

Parke Davis pointed out that in the leavepiece the claim was not adjacent to the graph but appeared on the opposite page. The graph clearly described the effects on LDL-cholesterol and not triglyceride-lowering effects. Each of the three stab points on the page stood alone. The two comparative claims clearly described the comparators involved. The triglyceride claim did not include a comparator but described triglyceride reductions which were significant compared to baseline for every Lipitor dose used in the CURVES study.

Parke Davis pointed out that statements used in material prepared by Merck Sharp & Dohme and by other companies such as "proven to improve survival" were not presented as compared to baseline or compared to no treatment. The company maintained that the claim did not suggest or imply that Lipitor was better than or stronger than any other intervention in relation to triglyceride lowering. The claim was not a hanging comparison.

## PANEL RULING

The objective of the CURVES study was to evaluate the comparative dose efficacy of atorvastatin compared with simvastatin, pravastatin, lovastatin and fluvastatin in patients with hypercholesterolaemia. The Panel noted that the authors of the CURVES study stated that it was not powered to detect differences in effects on triglycerides. The patient population studied consisted mostly (74%) of patients with elevated cholesterol without elevated triglycerides. Atorvastatin 10, 20 and 80mg produced numerically, but not statistically, greater reductions in triglycerides than the other statins at milligram-equivalent doses and statistically greater reductions in triglycerides at the 40mg dose. The Panel noted that Lipitor was indicated for the reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in patients with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or mixed hyperlipidaemia.

The Panel considered that the context of the claim and the impression from the material were important factors in considering this allegation. The two preceding claims which referred to advantages of Lipitor compared to the other products in the CURVES study were clearly comparative claims. The products were named and the p values for the differences were given. The claim at issue did not mention any comparators. Nonetheless the Panel considered that the claim was misleading as in the leavepiece it was referenced to a comparative study and in both the leavepiece and the mailing it appeared beneath two claims and a heading relating to the CURVES study. The impression given was that it related to a comparison of Lipitor with pravastatin, fluvastatin and simvastatin and not a comparison of Lipitor treatment with baseline. The Panel therefore ruled a breach of Clause 7.2 of the Code.

## APPEAL BY PARKE DAVIS AND PFIZER

Parke Davis did not believe that the context of this claim and its proximity to certain LDL-cholesterol lowering data from the CURVES study created a misleading impression. The main purpose of the CURVES leavepiece was to provide "top-line" information on the results of the CURVES study with respect to LDL-cholesterol.

Parke Davis acknowledged that the CURVES study was not powered to detect differences in effects on triglycerides; however, the CURVES study did demonstrate statistically significant reductions in triglyceride levels at all dosages of atorvastatin studied. Further, atorvastatin was licensed for "... reduction of total cholesterol ... ... and triglycerides ..." (Lipitor SPC). The claim at issue was simply a statement of fact that was adequately supported by the reference to the CURVES study. Where Parke Davis had, in its materials, made numerical claims relating to triglyceride lowering efficacy these had been supported by appropriate studies. For example, Dart *et al*, Bertolini *et al* and Schrott *et al* (formerly Gmerek).

The Panel and the Appeal Board had, in fact, previously ruled in favour of the claim that atorvastatin reduced cholesterol and triglycerides more than any other statin (Cases AUTH/525/4/97 and AUTH/526/4/97). This claim was supported by the studies cited as Bracs and Ergos and now published as Dart *et al* and Bertolini *et al*.

The claim quite clearly did not make a comparison to other statins – implicit or otherwise. The claim was very distinct from the two preceding claims, which were quite clearly comparative. Unlike these two other claims, the claim at issue did not contain the words "compared to" and it did not describe the other products being compared. The claim at issue was therefore not a hanging comparison as suggested by Merck Sharp & Dohme. A hanging comparison would have to state "... better or stronger or suchlike without stating that with which the medicine is compared ..." (Clause 7.2 – supplementary information). Indeed, this claim had been in use since the launch of atorvastatin in February 1997 and had withstood scrutiny by the medical community which, Parke Davis firmly believed, had not mis-interpreted the context of this claim which Merck Sharp & Dohme had found to be so objectionable. As it stood no reasonable reader could be misled. Parke Davis therefore considered the claim at issue not to be in breach of Clause 7.2.

## APPEAL BOARD RULING

The Appeal Board noted that the purpose of both the

leavepiece and the mailing was to inform the reader of the results of the CURVES study. The first piece of information given was the aim of the study which was to evaluate the comparative dose efficacy of Lipitor, pravastatin, simvastatin and fluvastatin at all licensed doses. The Appeal Board considered that the inside pages of the leavepiece and the results page of the mailing would be read in the light of the stated aim of the CURVES study. The first two claims clearly compared the results obtained with Lipitor with those obtained with the other statins in line with the stated aim of the study. The Appeal Board noted that the claim in question "Lipitor produced significant reductions in triglycerides" made no direct comparison with other statins but appeared beneath two claims and a heading relating to the CURVES study. The claim in the leavepiece was referenced to the CURVES study. Given the aim of the study the Appeal Board considered that most readers would view it as a comparative claim versus the other statins. This was not so. The Appeal Board considered that, given the context within which it was written, the claim was misleading and upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal on this point failed.

### 2 Claim "Lowers triglycerides by up to 45%"

The claim appeared as one of five bullet points above the prescribing information in both the leavepiece and the mailing. The claim was referenced to Gmerek (1996) and data on file Parke Davis.

#### COMPLAINT

Merck Sharp & Dohme alleged that the claim exaggerated the triglyceride lowering abilities of Lipitor. The claim was based on results from a subgroup of 12 patients taking 80mg Lipitor daily in a separate study published in abstract form only (Gmerek *et al* (1996)) and data on file). Merck Sharp & Dohme stated that the claim ignored the larger published body of evidence from the CURVES study itself around which the rest of the material was designed. In this study 61 patients who received 40mg Lipitor had a reduction in triglycerides of 32% (80mg atorvastatin produced no extra benefit). The company could see no valid reason why the results of a larger published trial were ignored in favour of those from a smaller unpublished trial. In addition other studies showed a maximum reduction in triglycerides of about 30% (Nawrocki *et al* (1995)) and Atorvastatin FOI package) and the SPC for Lipitor suggested that the maximum reduction was 33%.

Merck Sharp & Dohme did not accept that it was sufficient to say that because the claim referred to "up to" it was not misleading. The percentage given must reflect what the clinician could expect in the main otherwise it was of no guidance to the clinician and could only mislead. Breaches of Clauses 7.2 and 7.8 of the Code were alleged.

#### RESPONSE

Parke Davis pointed out that the materials had included this exact claim since launch. The company stated that the complainant referred to the Nawrocki *et al* study which had been in the public domain since before the launch of Lipitor and was described in the SPC. This dose ranging study evaluated the efficacy of Lipitor in patients with pure hypercholesterolaemia. The company submitted that one would not necessarily expect to be able to draw efficacy conclusions regarding triglyceride lowering from this patient population. The CURVES study was not designed to examine triglyceride effects per se. The mean baseline triglyceride levels in patients recruited into the study were between 1.66 - 2.26mmol/l and in over 90% of patients the level was below 2.0mmol/l. At these levels hypercholesterolaemic patients would not be considered to be additionally hypertriglyceridaemic. Thus the CURVES study was not designed to evaluate the range of triglyceride responses expected in these patients. The claim did not exaggerate the benefits reported in patients with mixed hyperlipidaemia. The claim was qualified by the phrase "up to" which made it clear that patients would not necessarily be expected to achieve this specific level of triglyceride alteration.

The data had recently been published in a peer review journal (Schrott *et al* (1998)) and fully supported the claim. The study was designed to evaluate the dose response effects of Lipitor on LDL-cholesterol and triglycerides in patients with a mixed profile (raised cholesterol and triglycerides over a six week period).

Parke Davis had conducted analysis of pooled data from all parallel group studies in patients with type IIa and IIb hyperlipidaemia with Lipitor (over 2000 patients in total) included in the licence application. Generally as expected the mean percentage reductions in triglycerides achieved with atorvastatin were dependent upon baseline triglyceride levels and the atorvastatin dose. In other words the higher the baseline triglyceride level or atorvastatin dose, the greater the percent reduction in triglycerides. At the 80mg dose there was a mean percentage reduction of 42% (SE 4.1) in the type IIa and IIb patients (n=40) who had baseline triglyceride levels of greater than or equal to 2.82mmol/l (250mg/dl). The range of triglyceride effects in this group ranged as far as or up to 76%. Thus, overall the results from the pooled analysis demonstrated triglyceride lowering effects which were consistent with the claim. Whilst there was a small difference between the mean derived from the pooled analysis and that from Gmerek now Schrott, the pooled analysis was consistent with and supported the claim. The claim reflected the maximum reduction but this was implicit within the claim. The company submitted that the use of the phrase "up to" was common within the pharmaceutical industry. The results were not unusual but were consistent with other triglyceride lowering effects seen with Lipitor.

The company submitted it was reasonable to base the claim on the Gmerek study since there were no significant data to refute it and the continuing analysis of data showed no inconsistencies with these findings.

#### PANEL RULING

The Panel examined the data relating to the effect of atorvastatin on triglyceride levels. The figure of a 45% reduction quoted in the promotional material came from

12 patients on an 80mg dose of atorvastatin. Patients recruited into the study had LDL-cholesterol levels between 4.1 and 6.5mmol and triglyceride levels of 4.5mmol or less. The data was originally in an abstract by Gmerek which had recently been published as a full paper by Schrott *et al.*

The CURVES study gave a figure of 32% (n=61) reduction in triglycerides at a dose of 40mg. The 80mg dose produced no extra benefit. The Panel noted that the patient population consisted mostly (74%) of patients with elevated cholesterol without elevated triglycerides. The entry criteria were LDL-cholesterol greater than or equal to 4.2mmol/l and triglycerides less than or equal to 4.5mmol/l.

The Nawrocki study gave a figure of a 33.2% reduction (n=10) with the 20mg dose. The patients in the study had elevated LDL-cholesterol and normal levels of triglycerides.

The atorvastatin FOI package (study 981-25) showed a reduction in triglycerides of 30% (n=57) at the 80mg dose. The study had the same entry criteria as the Gmerek study with LDL-cholesterol greater than 4.2mmol/l and triglycerides of less than 4.5mmol/l.

The Panel noted that the pooled analysis data submitted by Parke Davis showed a reduction of 42% in patients with baseline triglyceride levels of greater than or equal to 2.82mmol/l. Finally the Panel noted that the SPC published in the ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1998/1999 contained a table of data detailing dose response in patients with primary hypercholesterolaemia. The table showed that a dose of 20mg produced the greatest reduction in triglycerides from baseline, a 33% reduction. Higher doses did not produce a greater fall in triglycerides, an 80mg dose produced a 27% reduction. The SPC stated that the results were consistent in patients with heterozygous familial hypercholesterolaemia, non familial forms of hypercholesterolaemia and mixed hyperlipidaemia.

The Panel noted that the claim "Lowers triglycerides by up to 45%" was based on a small study the results for which were inconsistent with the information given in the SPC and other data. The Panel considered that the claim was not a balanced reflection of the all the available evidence. The Panel therefore ruled a breach of Clause 7.2 of the Code.

## APPEAL BY PARKE DAVIS AND PFIZER

As mentioned in its initial response, Parke Davis was surprised that Merck Sharp & Dohme had only now chosen to challenge this claim which had, in fact, formed part of the promotion of Lipitor since its launch.

The claim at issue referred to a maximal effect on triglyceride lowering by containing the phrase "...up to ...". This qualification made it clear to the reader that patients would not necessarily be expected to achieve this specific level of triglyceride alteration. This claim was not only supported by a peer reviewed study but was also borne out by evidence on the effects of atorvastatin on triglycerides from a meta-analysis. This represented a wealth of triglyceride lowering data from 20 clinical trials, involving over 2000 patients with a broad range of baseline triglyceride levels. Parke Davis stressed that these patients and the studies included were not selectively chosen, indeed they represented the full data submitted in the licence application to the MCA. The data for those patients receiving atorvastatin 80mg/day was naturally relatively limited (n = 40), because most patients achieved their target cholesterol and triglyceride reductions at lower dosages. The cited reference reported on the triglyceride lowering effects of atorvastatin in a specific peer reviewed study.

Much of the published data regarding the effects of atorvastatin on triglycerides was derived from clinical studies involving purely hypercholesterolaemic patients (ie those patients with raised cholesterol but without raised triglycerides). Just as one would expect an antihypertensive medication to provide only minimal reductions in blood pressure in normotensive patients, it was also reasonable to expect atorvastatin to provide more modest reductions in triglycerides in those patients with minimal elevations in triglycerides. Hence the reason for marginal and non-dose related effects of atorvastatin on triglyceride levels in studies which did not involve patients with significantly raised triglyceride levels. As a patient's baseline triglyceride level increased the effect of atorvastatin intervention on this parameter became more pronounced. This consideration was critical when the effects of atorvastatin on triglycerides were examined in the context of this claim.

Merck Sharp & Dohme suggested that Parke Davis was ignoring a larger body of evidence. Whilst there continued to be more data generated for atorvastatin the studies cited by Merck Sharp & Dohme did not alter Parke Davis' experience with regard to triglyceride lowering efficacy. The data Merck Sharp & Dohme had selectively cited pertained mainly to hypercholesterolaemic patients and not patients with clinically relevant raised triglycerides. The Nawrocki *et al* study was the dose-ranging study cited in the SPC for atorvastatin. This study evaluated the efficacy of atorvastatin in patients with baseline triglyceride levels which were near normal. As explained above, Parke Davis would not expect to be able to draw efficacy conclusions regarding triglyceride lowering solely from this study. The CURVES study, which was also mentioned by Merck Sharp & Dohme, was again not designed to examine triglyceride effects of atorvastatin *per se*. The mean baseline triglyceride levels in patients recruited into this study were between 1.66-2.26 mmol/l and in over 90% of patients the level was below 2.0 mmol/l, a clinically acceptable level. An analysis involving this selected patient group would not be appropriate to examine effects on the range of triglyceride lowering that atorvastatin could produce when including patients with raised triglycerides as well as raised cholesterol.

Parke Davis believed that its cited data for lowering triglyceride levels by up to 45% was robust support for this claim. Merck Sharp & Dohme cited selected studies, which did not contain an appropriate patient population to evaluate the triglyceride lowering effect of atorvastatin, as explained above. Parke Davis cited an appropriate study whose results were borne out by evidence from a meta-analysis of some 20 different studies. Generally, as

one would expect, mean percent reductions in triglycerides achieved with atorvastatin were dependent upon baseline triglyceride levels and the dose of atorvastatin given (ie the higher the baseline triglyceride level or atorvastatin dose, the greater the percent reduction in triglycerides). At the 80mg dose there was a mean percentage reduction of 42% (SE 4.1) in the type IIb patients (N = 40) who had baseline triglyceride levels of > 2.82 mmol/l (250mg/dl). As would be seen from a table which Parke Davis provided, the range of the triglyceride modifying effect in this patient group ranged up to minus 76%. Thus overall the results from this analysis involving over 2000 patients demonstrated triglyceride-lowering effects that were fully consistent with the claim. Whilst there was a small difference between the mean Parke Davis had derived from the analysis and that from Gmerek (now Schrott), the analysis was consistent with, and lent further support, to the claim.

The claim which stated "... by up to 45%" did reflect the maximum reduction, but that fact was implicit within the claim. Such use of the descriptive phrase "up to" was common within the industry. Moreover, these effects were not unusual but consistent with triglyceride lower effects, which had been seen in a whole range of patients treated with atorvastatin.

Parke Davis considered it perfectly reasonable to base the claim on the Gmerek (Schrott) study since there was no significant data to refute it; Parke Davis believed this to be a critical factor for not amending the claim. Parke Davis had demonstrated that its continuing analysis of the data showed no inconsistencies with the published findings on which the claim was based. Parke Davis continued to assess new data, however it would only amend a claim if these data suggested the claim was unrepresentative and no longer valid. In a previous case (Cases AUTH/525/4/97 and AUTH/526/4/97) it was not considered necessary to modify a claim on the basis that inclusion of further data slightly altered the figures in the claim. In this case Parke Davis' assessment of all available data was consistent with the findings on which the claim of "up to 45%" triglyceride lowering was originally based.

## APPEAL BOARD RULING

The Appeal Board noted that the back page of the mailing and the leavepiece listed a number of general claims regarding the efficacy, tolerability and cost of Lipitor therapy. Lipitor had a range of doses. The usual starting dose was 10mg daily but this could be increased to 80mg. The claim which preceded the claim in question stated that 67-95% of patients reached their LDL-cholesterol lowering goals at the 10mg once daily starting dose. In the Appeal Board's view, most patients would thus be treated with 10mg Lipitor daily. In this regard the Appeal Board noted the representatives' answer to a question indicated that 70-80% of patients would be on a dose of 10mg.

The Appeal Board noted that the claim in question "Lowers triglycerides by up to 45%" was based on an 80mg per day dose. A 45% reduction in triglycerides was thus a specific result using a specific, high dose of Lipitor. The Appeal Board considered that, given that the preceding claim referred to a 10mg once daily dose, some readers would assume that, without any indication to the contrary, the claim in question also related to that dose which was not so. The Appeal Board considered that without further explanation, the claim would mislead readers as to the degree that triglycerides levels might be lowered using the starting dose of Lipitor. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal on this point failed.

**Complaint received** **3 July 1998**

**Case completed** **14 October 1998**

CASE AUTH/737/7/98

# FORMER HEALTH SERVICE MANAGER v MERCK SHARP & DOHME

## Singulair advertisement in NHS Confederation Commemorative Diary

**A former health service manager complained about an advertisement for Singulair (montelukast), issued by Merck Sharp & Dohme which had appeared in the NHS Confederation Commemorative Diary for 1999. The diary had been distributed at a conference celebrating the 50th anniversary of the NHS. The complainant alleged breaches of the Code because it was an advertisement for a prescription only medicine which was not appropriate for the audience.**

**The Panel noted that the diary was a specialist title and was not aimed at the general public. The key factor was to whom a publication was aimed rather than whether it could be obtained by the general public. The Panel did not accept that the advertisement was an advertisement to the public as alleged. The diary was an acceptable vehicle for advertisements for prescription only medicines and no breach was ruled in that regard.**

**The Panel considered that the majority of the recipients of the diary would have been management/administrative personnel. The advertisement was an abbreviated advertisement and bore only a limited amount of text. The Panel considered, however, that the claims "Add-on therapy for mild to moderate chronic asthma" and "A single tablet-a-day helps control chronic asthma" were oriented towards clinicians. The advertisement had not been tailored to the audience to which it was directed and a breach of the Code was ruled.**

A former health service manager complained about an abbreviated advertisement which appeared in the NHS Confederation Commemorative Diary for 1999. An advertisement for Singulair (Montelukast)(ref 1-99 SGA.97.GB.13187.J), issued by Merck Sharp & Dohme Limited, featured a boy holding a ball and sitting on a man's shoulders. The text said "Add-on therapy for mild to moderate chronic asthma" and "A single tablet-a-day helps control chronic asthma". "1 tablet daily" was incorporated into the product logo. There were no other claims.

### COMPLAINT

The complainant stated that the advertisement for Singulair appeared in a free, give away, diary from the NHS Confederation. The Confederation represented trusts and purchasing commissions in the NHS with a management bias. The complainant could see no attempt to tailor the advertisement to the audience. He alleged that it breached Clauses 12.1 and 20.1 of the Code.

### RESPONSE

Merck Sharp & Dohme refuted any suggestion that the placing of the Singulair abbreviated advertisement constituted a breach of Clause 12.1 and/or Clause 20.1.

In the course of the complaint, the complainant had stated that the Confederation represented trusts and purchasing commissions in the NHS with a management bias. Merck Sharp & Dohme contended that this supported its argument that the likely recipients of the diary formed a wholly appropriate audience within the meaning of the supplementary information to Clause 1.1 which allowed promotion of medicines to "... appropriate administrative staff". Merck Sharp & Dohme therefore denied any breach of Clause 20.1 as this was not promotion to the general public but to an appropriate professional audience. As the Confederation was made up of trusts and purchasing commissions then this was precisely the professional audience which would reasonably be expected to satisfy Clause 1.4 of the Code, ie "... any other persons who in the course of their professional activities may prescribe, supply or administer a medicine".

With regard to the allegation of a breach of Clause 12.1, Merck Sharp & Dohme submitted that the audience was entirely appropriate. As for the specific allegation of no "tailoring", Merck Sharp & Dohme submitted that in its opinion this was a wholly appropriate advertising medium for the professional audience who would be likely recipients of the diary. Furthermore, an abbreviated advertisement in the context of a number of other advertisements was specifically allowable in publications such as diaries as was explained in the supplementary information to Clause 5.2.

It was Merck Sharp & Dohme's understanding that it was approached by the NHS Confederation via a third party to be offered the opportunity to place an advertisement in the diary. Some 2000 diaries were produced. The diary was included in the delegate pack for attendees at the "All Our Tomorrows" conference at Earl's Court 1 to 3 July 1998 held as part of the celebration of the 50th anniversary of the NHS.

### PANEL RULING

The Panel noted that Clause 1.1 of the Code stated that the Code applied to the promotion of medicines to members of the UK health professions and to appropriate administrative staff. The relevant supplementary information referred to Clause 12.1 which required that promotional material should only be sent or distributed to those persons whose need for, or interest in it, could reasonably be assumed. The supplementary information to Clause 12.1 stated that promotional material should be tailored to the audience to whom it was directed.

The Panel noted that there had been previous cases concerning advertisements for prescription only medicines in a publication for healthcare workers. In Case AUTH/145/4/94 the Panel had considered that the advertisement was not an advertisement to the public as alleged and that the publication was an acceptable vehicle for advertisements of prescription only medicines. In another more recent case, Case AUTH/720/6/98, the Panel had considered that the advertisement was not an advertisement to the public and that the journal involved

was an acceptable vehicle for advertisements of prescription only medicines but had, however, ruled a breach of Clause 12.1 of the Code as the wording of the advertisement had not been tailored to the audience.

The Panel examined the diary now before it. The diary was a specialist professional title and was not aimed at the general public. The Panel considered that the key factor was to whom the publication was aimed rather than whether it could be obtained by the general public. The Panel did not accept that the advertisement was an advertisement to the public as alleged and considered that the diary was an acceptable vehicle for advertisements for prescription only medicines. The Panel therefore ruled no breach of Clause 20.1 of the Code.

The Panel then considered whether the content of the advertisement was suitable for those who had received the diary. The recipients had been those attending the "All Our Tomorrows" conference held as part of the celebration of the 50th anniversary of the NHS. The NHS Confederation represented trusts and purchasing commissions in the NHS The Panel considered that the majority of the recipients would have been management and administrative personnel.

The advertisement was an abbreviated advertisement and bore only a limited amount of text. The Panel considered, however, that the claims "Add-on therapy for mild to moderate chronic asthma" and "A single tablet-a-day helps control chronic asthma" were orientated towards clinicians. The advertisement had not been tailored to the audience to which it was directed. A breach of Clause 12.1 of the Code was ruled.

**Complaint received** **3 July 1998**

**Case completed** **8 September 1998**

---

**CASE AUTH/738/7/98** *NO BREACH OF THE CODE*

# FORMER HEALTH SERVICE MANAGER v BSIA

## Pylobactell advertisement in HealthCARE today

**A former health service manager complained about an advertisement for Pylobactell, a $^{13}$C-urea breath test, issued by BSIA, which had appeared in HealthCARE today, alleging that it was in breach because it was an advertisement for a prescription only medicine and because the content of the advertisement was not appropriate for the audience.**

**The Panel noted that the journal was a specialist title and was not aimed at the general public. The key factor was to whom a publication was aimed rather than whether it could be obtained by the general public. The Panel did not accept that the advertisement was an advertisement to the public as alleged. The journal was an acceptable vehicle for advertisements for prescription only medicines and no breach was ruled in that regard.**

**The readership of the journal would be mainly administrative and general management personnel. The advertisement included information related to budgets and resources. It was not specifically orientated towards clinicians. The Panel considered that the information was not unacceptable in these circumstances and ruled no breach of the Code.**

A former health service manager complained about an advertisement which appeared in HealthCARE today - The Journal for NHS boards, July/August 1998. An advertisement for Pylobactell, issued by BSIA Limited, featured a photograph of the product and its pack with the texts "$^{13}$C-Urea Breath Test", "The gold standard solution for detection of active *Helicobacter pylori* infection", "Precise – non invasive – easy to use – rapid – cost effective" and "Approved in all EU countries". The only other copy was the prescribing information and company details.

BSIA, although not a member of the ABPI, agreed to comply with the Code and accept the jurisdiction of the Authority.

### COMPLAINT

The complainant alleged that the advertisement breached Clauses 12.1 and 20.1 of the Code of Practice. He could detect no attempt to tailor the advertisement to the audience.

On the wider issue of what constituted "appropriate administrative staff", the complainant said that the make-up of the journal's readership was 84% who had no conceivable contact or influence over prescribing issues and 14% who, given the most generous interpretation of their likely job specification, might have an interest, but mostly, no influence.

In this context, what did "manage the provision of healthcare" mean? A car park attendant was part of the hospital team. In the complainant's view this got into the realms of farce.

### RESPONSE

BSIA stated that HealthCARE today was a journal specifically aimed at the executive and non executive directors of NHS boards. The circulation was approximately 9000. The publication was not aimed at, nor was it readily available by sale or any other route, to the general public.

BSIA submitted that the NHS board members, which included medical directors, were important decision-makers. They worked with health authorities and were responsible for hospital policies on patient management and spending.

BSIA stated that the successful and cost effective management of *Helicobacter pylori* was currently a very important and topical issue. As a result the NHS executives and in particular the medical directors had an active interest in this area. The advertisement was aimed at informing the audience that the $^{13}$C breath test was the

'gold standard' for active *H.pylori* detection and that it was cost effective to use.

Therefore BSIA did not consider that it was in any way in breach of either Clause 12.1 or Clause 20.2 of the Code.

## PANEL RULING

The Panel noted that Clause 1.1 of the Code stated that the Code applied to the promotion of medicines to members of the UK health professions and to appropriate administrative staff. The relevant supplementary information referred to Clause 12.1 which required that promotional material should only be sent or distributed to those persons whose need for, or interest in it, could reasonably be assumed. The supplementary information to Clause 12.1 stated that promotional material should be tailored to the audience to whom it was directed.

The Panel noted that there had been previous cases concerning advertisements for prescription only medicines in a publication for healthcare workers. In Case AUTH/145/4/94 the Panel had considered that the advertisement was not an advertisement to the public as alleged and that the publication was an acceptable vehicle for advertisements of prescription only medicines. In another more recent case, Case AUTH/720/6/98, the Panel had considered that the advertisement was not an advertisement to the public and that the journal involved was an acceptable vehicle for advertisements of prescription only medicines but had, however, ruled a breach of Clause 12.1 of the Code as the wording of the advertisement had not been tailored to the audience.

The Panel examined the journal now before it. HealthCARE today – The Journal for NHS boards was a specialist professional title and was not aimed at the general public. The Panel considered that the key factor was to whom the publication was aimed rather than whether it could be obtained by the general public. The Panel did not accept that the advertisement was an advertisement to the public as alleged and considered that the publication was an acceptable vehicle for advertisements for prescription only medicines. The Panel therefore ruled no breach of Clause 20.1 of the Code.

The Panel then considered whether the content of the advertisement was suitable for the readership of the journal which would mainly be administrative and general management personnel with only a limited number of clinicians.

That Panel noted that the product was a diagnostic test. It was classified as a medicine because the tablet involved had to be taken by the patient, rather than it being an entirely *in vitro* test. The Panel considered that the information given was not unacceptable in these particular circumstances. The advertisement included information related to budgets and resources. It was not specifically orientated towards clinicians. The Panel ruled no breach of Clause 12.1 of the Code.

The Panel noted the complainant's general comments about the management of healthcare and the reference to the car park attendant as being part of the healthcare team but considered that this showed that the Code's requirements in this regard had to be applied in a sensible, flexible and realistic manner.

**Complaint received** **3 July 1998**

**Case completed** **8 September 1998**

CASE AUTH/739/7/98

# GENERAL PRACTITIONER v BAYER

## Promotion of Ciproxin

**A general practitioner complained about a cost comparison in a Ciproxin detail aid and a claim in a Ciproxin leaflet issued by Bayer. The complainant had asked a Bayer representative whether Ciproxin, in normal doses, was cheaper than co-amoxiclav. The Bayer representative had said that it was and had showed the complainant the detail aid and leaflet. The complainant alleged these were misleading as the cost comparison chart did not compare the usual doses, ie co-amoxiclav at 375mg tds and Ciproxin at 500mg bd, and at this dose Ciproxin was considerably more expensive.**

**The Panel considered that the cost comparison chart was misleading. The highest dose of Ciproxin had not been included and nor had the fact that the duration of treatment could extend to ten days. The highest doses of competitor products had been given but not the maximum treatment lengths. The Panel considered that the chart was too simplistic given the information in the summaries of product characteristics. A breach of the Code was ruled.**

**On appeal by Bayer the Appeal Board considered that the cost comparison chart failed to adequately reflect the information in each product's SPC regarding dosage and duration of treatment. The Appeal Board upheld the Panel's ruling of a breach of the Code**

**The Panel considered that the claim "competitively priced therapy" in the leaflet was not unacceptable and ruled no breach of the Code.**

A general practitioner complained about a page in a Ciproxin detail aid (ref 9BCPT891) and a Ciproxin leaflet (ref 9CIPR030) both issued by Bayer plc, Pharmaceutical Division.

The page in the detail aid was entitled "Rapid, reliable and competitively priced" and featured a cost comparison of Ciproxin (250mg bd x 5 days = £7.50 and 500mg bd x 5 days = £14.20), co-amoxiclav (375mg tds x 7 days = £9.79 and 625mg tds x 7 days = £15.73) and clarithromycin (250mg bd/500mg od x 7 days = £11.24 and 500mg bd x 7 days = £22.49) on three separate bars. The cost comparison was headed "Cost per course" and the heading referred readers to a footnote which stated "These costs do not reflect the maximum dosages nor the maximum treatment lengths for these agents".

The leaflet did not mention the competitor products or make any specific claim regarding cost. The only claim of this nature was "Competitively priced therapy".

### COMPLAINT

The complainant stated that during a presentation from a Bayer representative the complainant asked if it was true, as he had been previously told by a representative of this company, that Ciproxin, in normal doses, was cheaper than co-amoxiclav. The complainant asked this specifically as he had contacted the co-amoxiclav representative who informed him that this was not true. The Bayer representative said yes it was and showed him the literature.

The complainant alleged that this was misleading as the normal dose of co-amoxiclav was 375mg tds and the normal dose of Ciproxin was 500mg bd for 5 days and at this dose Ciproxin was considerably more expensive. It might be that people disagreed with what he would regard as a normal dose, but he personally believed that the way this information was represented was misleading and asked that action was taken to ensure the company withdrew this literature.

### RESPONSE

Bayer stated that the page in the Ciproxin detail aid, showed the costs of the 250mg and 500mg packs of Ciproxin as licensed. The licensed packs of co-amoxiclav and clarithromycin were similarly presented. The page did not give a direct comparison between any particular dosage but merely showed the costs of the packs available. The cost comparison also carried a disclaimer stating that the "... costs do not reflect the maximum dosages nor the maximum treatment lengths ...". The costs had been referenced to MIMS October 1997 and were correct at the time the item was produced. The artwork similarly presented the information in a clear, fair and balanced way and Bayer believed there was no breach of the Code.

Bayer stated that the claim in the leaflet that Ciproxin was "Competitively priced" did not mean that it was the cheapest therapy but that it was priced within the same range as its competitors. Bayer therefore believed that this item was consistent with the Code.

Bayer provided a copy of a memorandum dated 16 July 1998 which it had sent to all of its representatives selling Ciproxin stating the intended use and interpretation that should be given to the costs of Ciproxin and its competitors as shown in the detail aid. Bayer hoped that this would prevent any misinterpretation in the future.

### PANEL RULING

The Panel noted that the detail aid as a whole was directed towards the use of Ciproxin in respiratory tract infections, principally bronchitis. The Panel noted that although, according to Bayer's submission, the cost comparison showed the price of the available packs of the product, the comparison was headed "Cost per course". No mention was made that costs were the cost of each pack. The Panel noted that beneath the cost comparison was the claim "A drug of choice in LRTIs [lower respiratory tract infections]." In the Panel's view the cost comparison chart would be taken to represent the cost of actually treating a patient with a lower respiratory tract infection.

The Panel referred to the summaries of product characteristics (SPCs) published in the ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1998-99. The Augmentin (co-amoxiclav)

SPC stated that for all infections the usual dose of the product was 375mg three times a day which could be increased to 625mg three times a day in severe infections. It was stated that the duration of therapy should be appropriate to the indication and should not exceed 14 days without review. (For dental infections the duration of therapy was given as 5 days). The Panel noted that the cost comparison chart showed the costs of both doses of co-amoxiclav over a seven day course.

The SPC for Klaricid (clarithromycin) stated that in patients with respiratory infections the usual dose was 250mg twice daily for one week which could be increased to 500mg twice daily for up to two weeks in severe infections. The Panel noted that the cost comparison chart showed the cost of the lower dose of clarithromycin as 250mg twice daily or 500mg once daily for one week. The Panel noted that the SPC did not mention a once daily dosage of 500mg although this was mentioned in MIMS July 1998. The upper dose of clarithromycin was given in the cost comparison as 500mg twice daily for one week.

The SPC for Ciproxin, supplied by Bayer, stated that the dose range for adults was 250-750mg twice daily. In acute infections, other than uncomplicated cystitis, the usual treatment period was given as 5-10 days. The Panel noted that the cost comparison chart showed the cost of Ciproxin 250mg twice daily for five days and 500mg twice daily for five days. The Panel noted that the cost of therapy with Ciproxin 750mg had not been shown.

The Panel considered that the cost comparison was misleading. The highest dose of Ciproxin had not been included nor the fact that the duration of treatment could extend to ten days. Although the highest doses of the competitors had been stated the maximum treatment lengths had not been given. The Panel considered that the chart was too simplistic given the information in the three SPCs. The Panel ruled a breach of Clause 7.2 of the Code.

The Panel considered that the claim "competitively priced therapy" on the leaflet was not unacceptable. It was not a claim that Ciproxin was the cheapest therapy and the lowest dose of Ciproxin (250mg bd for 5 days) cost less than the lowest dose of clarithromycin (250mg bd for 7 days). The Panel therefore ruled no breach of the Code.

## APPEAL BY BAYER

Bayer stated that it was appealing against the decision that the cost comparison in the Ciproxin detail aid was in breach of Clause 7.2 of the Code.

Bayer stated that it held the opinion that this page of the detail aid did not give a direct comparison between any particular dosage of the three antibiotics. It also noted that the Panel had already acknowledged that this piece was principally directed to the use of antibiotics in the treatment of bronchitis.

Bayer's representatives were trained to discuss this with the general practitioner according to his/her usual prescribing practices. In the case in question therefore, Bayer acknowledged that the representative should have discussed the cost implication from the table, relevant to the GP's specific prescribing as indicated during the interview.

The costs in the detail aid were calculated using the most commonly prescribed course lengths, supported by information obtained via DIN-Link MAT June 1998 for the diagnosis of LRTI. These referred to 5 and 7 day courses for Ciproxin and co-amoxiclav/clarithromycin respectively.

In addition, the disclaimer clearly stated that '... these costs do not reflect the maximum dosages nor the maximum treatment lengths for these agents ...'. Should the prescribing physician wish to give courses of therapy longer than those indicated in the chart, Bayer's representative would assist him or her to calculate accordingly.

With regard to dosage, Bayer submitted that the chart accurately reflected the great majority of usage (DIN Link) of the antibiotics in the indication detailed (respiratory tract infection), eg the Ciproxin 750mg dosage accounted for only 1.5% of prescriptions. On these bases Bayer considered that the chart was not misleading to the prescriber.

## APPEAL BOARD RULING

The Appeal Board noted that the appeal related solely to the detail aid, the complainant having accepted the ruling of no breach in relation to the leaflet.

The Appeal Board considered that the cost comparison chart gave the impression that the costs stated represented the actual cost of treating a patient with a lower respiratory tract infection. The cost comparison chart failed to adequately reflect the information in each product's SPC regarding the dosage and duration of treatment. The chart was too simplistic given the information in the SPCs. The Appeal Board considered the chart misleading and upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal therefore failed.

**Complaint received** **10 July 1998**

**Case completed** **14 October 1998**

CASE AUTH/740/7/98

# GENERAL PRACTITIONER v ASTRA

## Losec advertisement

**A general practitioner complained about an advertisement for Losec issued by Astra. The advertisement stated that Losec could now be used in children with severe ulcerating reflux oesophagitis and included the claims "Outstanding acid suppression" and "Outstanding healing". The complainant alleged that these claims were exaggerated and inaccurate.**

**The Panel noted that Losec had some licensed indications which set it apart from the two other proton pump inhibitors (PPIs). It was the only PPI which could be used in children. Losec was also the only PPI licensed for NSAID - associated gastric and duodenal ulcer healing and prophylaxis in patients with previous gastroduodenal lesions and for prophylaxis of acid aspiration.**

**The Panel noted that the advertisement featured a photograph of a young boy and promoted the use of Losec in children with severe ulcerating reflux oesophagitis. The prescribing information covered all licensed indications although details regarding paediatric dosing had been highlighted. The claims in question had been separated from the main body of text by the Losec logo and the Panel considered that they would be seen as general claims for the product and not specifically relating to the use of Losec in children.**

**The Panel considered that there was insufficient data to differentiate Losec from all other treatments to the extent implied by the use of the word "outstanding". The claims were exaggerated and misleading and a breach of the Code was ruled.**

A general practitioner complained about a journal advertisement for Losec (omeprazole) (ref LOS ADV 3191) issued by Astra Pharmaceuticals Ltd. The advertisement stated that Losec was now licensed for use in children and included the claims "Outstanding acid suppression" and "Outstanding healing". The advertisement had appeared in a number of medical and pharmacy journals.

### COMPLAINT

The complainant alleged that the advertisement stated that Losec was "outstanding", which implied that it was a superior product to others available (Oxford Dictionary). The complainant thought that this was not so, and so the claim was exaggerated and inaccurate. As far as the complainant was aware, this product had never been shown to be better than lansoprazole in any parameter measured, and, in fact, in some studies, lansoprazole had been shown to be more effective than omeprazole.

### RESPONSE

Astra stated that the complainant alleged that the use of the word "outstanding" in this advertisement implied "a superior product to others available" and made an "exaggerated and inaccurate" claim for the product. Astra said that it would be grateful if the Panel could request clarification from the complainant as to which studies he/she referred to in the point "lansoprazole has been shown to be more effective than omeprazole", as Astra would then be able to comment specifically on those.

The message of the advertisement was that Losec had been granted a new licence in children with severe ulcerating reflux oesophagitis. To obtain a licence in children, it was necessary to provide the licensing authority with specific data in children supported by considerable evidence on efficacy and safety in order to satisfy its stringent requirements in this particular patient group. To reflect this, the advertisement contained the statement "Outstanding acid suppression. Outstanding healing". There were different dictionary definitions of "outstanding": an alternative definition to that cited by the complainant was "conspicuous, or eminent because of excellence, or remarkable in a specified field" (Oxford Encyclopaedic English Dictionary). In the context of this advertisement, this was the message which the statement was intended to convey. The statement related to Losec as an antisecretory agent with no comparative reference to any specific antisecretory agent.

Astra believed that the use of the claims "Outstanding acid suppression" and "Outstanding healing" were supportable for the following reasons:

### General

- Losec was the first proton pump inhibitor (PPI) to be licensed in the UK, in 1989. As such it was a major therapeutic advance. Prior to this $H_2$ antagonists, eg cimetidine and ranitidine, were the most effective treatments for acid-related disorders. Two further PPIs had since been licensed in the UK – lansoprazole (1994) and pantoprazole (1996).

  Losec was the only PPI licensed for children from 2 years old with severe ulcerating reflux oesophagitis; no other PPI had a licence in any paediatric population. This further emphasised the point already mentioned above, that to obtain a licence in children it was supported by considerable evidence on efficacy and safety in order to satisfy the licensing authority's stringent requirements. Of the $H_2$ antagonists, only the first two, cimetidine and ranitidine, had a paediatric licence, reflecting their considerable efficacy and safety experience; others (nizatidine, famotidine) did not.

- Losec was the only PPI to be licensed in the following other indications:
  - Non-steroidal anti inflammatory drug (NSAID)-associated gastric and duodenal ulcer healing
  - NSAID-associated gastric and duodenal ulcer prophylaxis in patients with previous gastroduodenal lesions
  - Prophylaxis of acid aspiration.
- Over 293 million treatment courses of Losec had been prescribed in more than 100 countries world-wide. There were over 8,000 published Losec references and

over 600 clinical trials involving over 45,000 individuals.

### Acid suppression

- Losec had clearly been shown to produce greater acid suppression than ranitidine or cimetidine (eg Jones *et al* 1987).
- Losec had a pronounced dose response in acid suppression throughout the therapeutic range. Up until January 1998 this had been investigated in 22 studies in healthy volunteers and patients with duodenal and gastric ulcers and reflux oesophagitis over a dose range of 10 to 40mg once daily, eg pH was maintained above 3 for 13.21, 19.10 and 21.45 hours respectively in duodenal ulcer patients on Losec 10mg, 20mg and 40mg once daily (Savarino *et al* 1994).
- There was a lack of dose response in acid suppression seen with pantoprazole above 40mg daily (Reill *et al* 1993).
- The dose response in acid suppression for lansoprazole had been examined in twelve studies (eg Seensalu *et al* 1995, Geus *et al* 1997) and two in patient subjects (eg Paoletti *et al* 1997). While a clear dose response could be seen with lansoprazole at doses from 15mg to 30mg daily, the dose response for lansoprazole at doses above 30mg daily (the standard healing dose for reflux oesophagitis) was less pronounced (Dammann *et al* 1993).

In summary, Losec had been shown in numerous studies to produce pronounced dose-related acid suppression in healthy subjects and in patients with acid-related disease. No other PPI had been studied as extensively and from the body of evidence in published references no other antisecretory agent had been consistently shown to produce superior acid suppression. There was thus adequate data to substantiate the statement that Losec offered "outstanding acid suppression".

### Clinical efficacy

Losec was licensed for:

- The healing and maintenance of healing of oesophageal reflux disease (GORD)
- The healing and maintenance of healing of duodenal ulcer
- The healing of gastric ulcer
- NSAID-associated gastric and duodenal ulcer healing
- NSAID-associated gastric and duodenal ulcer prophylaxis in patients with previous gastroduodenal lesions
- Prophylaxis of acid aspiration
- Children from 2 years old with severe ulcerating reflux oesophagitis (no other PPI had a licence in any paediatric population).

In a large number of studies, Losec had been shown to provide a consistent dose-dependent response across this wide range of indications. With specific reference to the efficacy of Losec in healing acid related disorders:

- Losec had been shown to be more effective in healing and maintenance of healing of reflux oesophagitis and in healing gastric and duodenal ulceration than $H_2$ agonists (eg Bate *et al* 1991, Bate *et al* 1990, Bardhan *et al* 1986, Walan *et al* 1989).
- Losec had been compared to other PPIs. Losec 20mg had been shown to be equivalent to lansoprazole 30mg and pantoprazole 40mg in healing of duodenal ulcer disease (Ekström *et al* 1992).
- Losec 20mg had been shown to have similar efficacy to lansoprazole 30mg (Hatlebakk *et al* 1993) and to pantoprazole 40mg in healing of GORD (Rehner *et al* 1995) and at higher doses, greater efficacy in the short-term maintenance of healing of severe, complicated reflux oesophagitis (Jaspersen *et al* 1998). Losec 20mg had also been shown to have similar efficacy to lansoprazole 30mg in the long-term maintenance of healing of reflux oesophagitis and superior efficacy to lansoprazole 15mg (Baldi *et al* 1996).
- Unlike Losec, neither of the other PPIs had an indication for use in the healing of NSAID-induced gastric and duodenal ulceration.
- Unlike Losec, neither of the other PPIs had a paediatric indication, such as healing of severe ulcerating reflux oesophagitis which was the subject of the advertisement.

In summary Losec was effective in healing a wide range of acid-related disorders including some for which the other PPIs were not licensed. In the indications for which the other PPIs were also licensed, there was no consistent evidence overall that either lansoprazole or pantoprazole had greater efficacy in healing and maintenance of healing than that achieved with Losec. There was clear evidence that Losec had superior efficacy in the healing and maintenance of reflux oesophagitis and healing of gastric and duodenal ulcer compared to the $H_2$ antagonists. There was thus adequate data to substantiate the statement that Losec provided "outstanding healing".

In conclusion, the data served to differentiate Losec sufficiently from other treatments for acid-related disorders in terms of acid suppression and healing to justify the use of the word "outstanding". Therefore, Astra did not accept that the claim was in breach of the Code, with particular reference to the requirements of Clauses 7.2, 7.3 and 7.8.

### PANEL RULING

The Panel noted that the dosage and administration section of the Losec data sheet included a reference to children over two years of age with severe ulcerating reflux oesophagitis. The Panel noted Astra's submission that Losec was the only proton pump inhibitor (PPI) of the three PPIs licensed in the UK which could be used in children. Such treatment should be initiated by a hospital based paediatrician.

The Panel noted Astra's submission that to obtain a licence in children it had to provide the licensing authority with specific data in children supported by considerable evidence on efficacy and safety. The data

sheet stated that in children over 2 years with severe ulcerating reflux oesophagitis, Losec was recommended for healing and symptom relief within the dose range of 0.7-1.4mg/kg daily to a maximum of 40mg/day, for 4-12 weeks. This was followed by "Data suggests that approximately 65% of children will experience pain relief on this dose regimen". The data sheet stated under the further information section that available data from children (1 year and older) suggested that the pharmacokinetics within the recommended doses were similar to those reported in adults.

The Panel noted that there were other differences between the licensed indications for Losec and those for the other proton pump inhibitors. Losec was the only proton pump inhibitor to be licensed for NSAID-associated gastric and duodenal ulcer healing, for NSAID-associated gastric and duodenal ulcer prophylaxis in patients with previous gastroduodenal lesions and for prophylaxis of acid aspiration.

The Panel noted that the advertisement was a double page spread. The left hand page featured a photograph of a young boy and a rabbit. The statement "The only everyday thing about Losec is the small people who take it" appeared prominently on the right hand page above the phrase "Now licensed for use in children with severe ulcerating reflux oesophagitis". The Losec logo appeared near the bottom of the right hand page followed by the claims, "Outstanding acid suppression." and "Outstanding healing.". The prescribing information ran down the outside edge of the right hand page.

The Panel noted that the copy of the advertisement promoted the use of Losec in children. The prescribing information covered all the uses of Losec although that part of the dosage and administration section detailing its use in children had been highlighted. The Panel noted that the claims in question were separated from the main body of text by the Losec logo. The Panel considered that the claims would be seen as general claims for the product and not specifically relating to the use of Losec in children.

The Panel considered that although Astra had some data to support the claims it was not sufficient to differentiate Losec from all other treatments to the extent implied by the use of the word "outstanding". The Panel considered that claims were exaggerated and misleading and breaches of Clauses 7.2 and 7.8 were ruled.

**Complaint received** **13 July 1998**

**Case completed** **21 September 1998**

---

**CASE AUTH/742/7/98** *NO BREACH OF THE CODE*

# GENERAL PRACTITIONER v SCHERING-PLOUGH

## Sampling of Elocon

**A general practitioner complained that one of his patients had received a free sample of Schering-Plough's Elocon (mometasone furoate), a prescription only medicine, when she had attended a national eczema day in Glasgow. It alarmed him that a patient could receive a potent steroid as a free sample, presumably without medical supervision.**

**The Panel noted that according to Schering-Plough's representative's account of the day, when the exhibition stand got busy samples were not removed from view as such but tubes were removed from boxes leaving empty boxes on the stand. The representative had confirmed her understanding that samples were not to be issued to members of the public and that signatures were to be obtained from health professionals for samples. The Panel examined the representative's sample receipt book but it was not helpful. The Panel considered that it was impossible to establish what had happened as the evidence was conflicting and ruled no breach of the Code.**

**The Panel was extremely concerned about the arrangements at the day which had been organised by a patient group and at which a significant proportion of those present would be patients. At such an event material on pharmaceutical company stands should be appropriate for the general public.**

### COMPLAINT

A general practitioner expressed his concern about the sampling of Elocon (mometasone furoate) by Schering-Plough Ltd. A patient of his with eczema, who was previously receiving clobetasone butyrate, had now requested a prescription for mometasone furoate ointment because when she attended a national eczema day at the Royal Concert Hall, Glasgow, in June 1998, she received a free sample of Elocon which she had tried and found to work well. In the circumstances the complainant had been happy to oblige with the continuation of this treatment. However the fact that the patient could receive a potent steroid as a free sample, and presumably without medical supervision, did alarm him.

When writing to Schering-Plough the Authority drew attention to Clauses 2, 9.1 and 17 of the Code.

### RESPONSE

Schering-Plough stated that investigation of the alleged incident had revealed that the company did attend the care day on 27 June 1998 in Glasgow as exhibitors. Schering-Plough gave specific instructions to its attending representative that samples were to be issued and signed for by members of the medical profession only. A copy of the instructions was provided.

A copy of the representative's account of the day was also provided. Schering-Plough submitted that as numbers of people visiting the stand increased the representative removed all samples from view. Moreover, the representative confirmed her understanding that samples were not to be issued to members of the public and that where samples were issued to qualified medical professionals, signatures were to be obtained. Schering-Plough believed, therefore, that its representative had acted in a responsible and professional manner and

complied with the requirements of the Code in all respects.

The original sample receipt book used at the meeting was provided for reference.

Schering-Plough stated that was possible that a member of the public had obtained a sample of Elocon at this meeting either by deception or from a medical colleague attending the meeting. Either way, Schering-Plough considered that it had operated in accordance with both the spirit and instruction of the Code at this meeting and that no breach of the Code could be ruled.

### PANEL RULING

The Panel examined the sample receipt book that had been provided by Schering-Plough. Three receipts were dated 27 June 1998, the day in question. One of the receipts had been signed by a male. It was impossible to identify the recipients of the other two samples.

The Panel noted that, according to the representative's account of the day, when the exhibition stand got busy samples were not removed from view as such but tubes were removed from boxes leaving empty boxes on the stand.

The Panel considered that on the evidence submitted it was impossible to establish the circumstances in which the patient had received a sample of Elocon. The complainant stated that the patient had been given a sample of a prescription only medicine. The company had denied that samples had been given to members of the public. Due to the conflict of evidence the Panel ruled that there had been no breach of the Code.

The Panel was extremely concerned about the arrangements in place for the care day. The Panel considered that it was inevitable that at such a day, organised by a patient group, a significant proportion of those present would be members of the public suffering from eczema. In such circumstances all material on pharmaceutical company stands had to be suitable for the general public. The Panel requested that Schering-Plough be reminded of the provisions of Clause 20.1 which prohibited the promotion of prescription medicines to the general public.

**Complaint received** **14 July 1998**

**Case completed** **24 August 1998**

---

**CASE AUTH/743/7/98**

# FORMER HEALTH SERVICE MANAGER v MERCK SHARP & DOHME

## Singulair advertisement in NHS conference papers

**A former health service manager complained about an advertisement for Singulair (montelukast), issued by Merck Sharp & Dohme, which had appeared in the papers for the conference "The NHS: All our Tomorrows A Golden Celebration for the National Health Service". The complainant alleged that it was in breach because it was an advertisement for a prescription only medicine and because the content of the advertisement was not appropriate for the audience.**

**The Panel ruled that the conference papers were targeted at a specialist audience and were not aimed at the general public. The key factor was the intended audience rather than whether they would be obtained by the general public. The Panel did not accept that the advertisement was an advertisement to the public as alleged. The conference papers were an acceptable vehicle for advertising for prescription only medicines and no breach was ruled in that regard.**

**The conference was primarily aimed at healthcare managers but, in the Panel's view, the advertisement was orientated towards clinicians. The Panel noted claims such as "improves control when used with an inhaled steroid" and "provides prophylaxis in exercise-induced asthma". The advertisement had not been tailored to the conference audience and a breach of the Code was ruled.**

A former health service manager complained about an advertisement which had appeared in conference papers for the conference "The NHS: All Our Tomorrows A golden celebration of the National Health Service" which had taken place at Earls Court in July 1998. An advertisement for Singulair (montelukast) (ref 04-99 SGA.97.GB.13017.J), issued by Merck Sharp & Dohme Limited, said "New from MSD", "The first once-daily leukotriene receptor antagonist for chronic asthma" and went on to list the benefits of Singulair in mild to moderate asthma. Above the prescribing information was stated "A single tablet-a-day helps control chronic asthma".

### COMPLAINT

The complainant said that the advertisement was taken from the conference papers of the 50th anniversary conference at Earls Court. He provided a copy of an editorial from the Health Service Journal which he said bemoaned the managerial nature of the conference. The complainant alleged that this was a blatant exploitation of the Code.

When writing to Merck Sharp & Dohme the Authority drew attention to the requirements of Clauses 12.1 and 20.1 of the Code.

### RESPONSE

Merck Sharp & Dohme refuted any suggestion that there had been a breach of Clause 12.1 and/or Clause 20.1 of the Code.

Merck Sharp & Dohme stated that the complainant attached an editorial from the Health Service Journal in support of his case that "... there is a blatant exploitation of the Code". While he selectively quoted the

"managerial" nature of the conference to presumably suggest that the advertisement was (i) promotion to the general public breaching Clause 20.1 and/or (ii) that it was inappropriate distribution of promotional material in breach of Clause 12.1, Merck Sharp & Dohme referred the Panel to the previous part of that sentence which stated, "The organisers failed to get the active participation of the other main health professions". The editorial itself stated that "Initial ambitions" had focused on attracting 4,000 paying delegates.

When Merck Sharp & Dohme was approached directly by the NHS Confederation to become a significant sponsor of the event it was led to believe that the Confederation was intending to attract a large number of delegates (around 5,000) which would include a significant number of clinicians and other health professionals as part of that target audience. Merck Sharp & Dohme understood that the event was advertised in leading professional journals such as The Lancet and the British Journal of General Practice.

Merck Sharp & Dohme contended therefore that there was no breach of Clause 20.1 as this was not promotion to the general public; it was promotion intended for a wide cross section of health professionals and health managers at the time that the company provided the Singulair advertisement to be included in the conference materials. The fact that the conference organisers failed to attract their original target audience was, Merck Sharp & Dohme submitted, outside of its control and the correct test to apply was what the target audience was intended to be. Merck Sharp & Dohme believed that it acted in good faith and had complied with that test.

If that argument was not accepted, the actual attendees were predominantly senior heath care managers and, therefore, an appropriate audience to promote to in accordance with Clause 1.4, ie "... any other persons who in the course of their professional activities may prescribe, supply or administer a medicine". Merck Sharp & Dohme denied any suggestion that this was promotion to the general public and, therefore, denied any breach of Clause 20.1.

Merck Sharp & Dohme submitted that the same argument should be addressed when considering Clause 12.1. Merck Sharp & Dohme's understanding was that a significant number of attendees were going to be physicians and other health professionals. The advertisement was appropriate in the light of the anticipated audience. The fact that the organisers were unsuccessful in their attempts to secure such a broad audience was beyond Merck Sharp & Dohme's reasonable control.

In any event it was Merck Sharp & Dohme's view that there was no breach of Clause 12.1 because even if consideration was restricted to the actual attendees, they were senior health managers and, therefore, naturally fell into "... those categories of persons whose need for and understanding of the information can reasonably be assumed".

**PANEL RULING**

The Panel noted that Clause 1.1 of the Code stated that the Code applied to the promotion of medicines to members of the UK health professions and to appropriate administrative staff. The relevant supplementary information referred to Clause 12.1 which required that promotional material should only be sent or distributed to those persons whose need for, or interest in it, could reasonably be assumed. The supplementary information to Clause 12.1 stated that promotional material should be tailored to the audience to whom it was directed.

The Panel noted that there had been previous cases concerning advertisements for prescription only medicines in a publication for healthcare workers. In Case AUTH/145/4/94 the Panel had considered that the advertisement was not an advertisement to the public as alleged and that the publication was an acceptable vehicle for advertisements of prescription only medicines. In another more recent case, Case AUTH/720/6/98, the Panel had considered that the advertisement was not an advertisement to the public and that the journal involved was an acceptable vehicle for advertisements of prescription only medicines but had, however, ruled a breach of Clause 12.1 of the Code as the wording of the advertisement had not been tailored to the audience.

The Panel examined the materials now before it. The conference papers were targeted at a specialist audience and were not aimed at the general public. The Panel considered that the key factor was the intended audience rather than whether they could be obtained by the general public. The Panel did not accept that the advertisement was an advertisement to the public as alleged and considered that the conference papers were an acceptable vehicle for advertisements for prescription only medicines. The Panel therefore ruled no breach of Clause 20.1 of the Code.

The Panel then considered whether the content of the advertisement was suitable for those who had attended the "All Our Tomorrows" conference and thus been in receipt of the conference papers. The Panel noted, from the conference papers, that the conference had been jointly organised by the NHS Confederation, the Institute of Health Service Management and the International Hospital Federation, all of which were bodies concerned with the management of healthcare. The Panel noted that although the organisers had sought the participation of other main health professionals, and some clinicians were expected to attend, the conference was nonetheless primarily aimed at healthcare managers.

In the Panel's view, the advertisement was orientated towards clinicians rather than towards administrators and managers. In this regard the Panel noted such as "improves control when used with an inhaled steroid" and "provides prophylaxis in exercise-induced asthma". The advertisement had not been tailored to the conference audience. A breach of Clause 12.1 of the Code was ruled.

**Complaint received** **15 July 1998**

**Case completed** **8 September 1998**

CASE AUTH/746/7/98

# GENERAL PRACTITIONER v KNOLL

## Conduct of a representative

**A general practitioner complained about a contract representative from the Trent sales force of Ashfield Healthcare. The representative had used his business card to write the following note to the GP "Please could you spare me a few minutes. I have a number of give-aways: umbrellas, lamps, minor op kits - if you are interested. Many Thanks".**

**The representative had been promoting two of Knoll Limited's products and so Knoll was responsible for the conduct of the representative as far as the Code was concerned.**

**The Panel considered that the note amounted to the representative offering the doctor inducements in order to gain an interview. A breach of the Code was ruled.**

A general practitioner complained about the activities of a representative from Trent, c/o Ashfield Healthcare Ltd. Ashfield confirmed that the representative was part of its Trent sales force, a contract sales force provided to Knoll Limited to promote its products, Protium and Gopten. The supplementary information to Clause 15 of the Code provided that companies employing or using contract representatives were responsible for their conduct and compliance with the Code. Knoll was thus responsible for the activities of the representative.

The complainant provided a photocopy of the representative's business card which bore the following handwritten note "Please could you spare me a few minutes. I have a number of give-aways: umbrellas, lamps, minor op kits – if you are interested. Many Thanks."

### COMPLAINT

The complainant stated that gradually the younger partners of the practice were agreeing with him and not wasting the scarce resources of doctor's time on listening to medical reps' sales talk and as they declined to see reps the bribes got bigger - the latest being golfing umbrellas, an expensive halogen lamp, or a minor surgery operating kit, or all three if they wished.

The complainant asked, " What price ethical medicine?"

### RESPONSE

Knoll stated that the representative was a relatively new representative and had not yet sat the ABPI examination. He admitted writing the note on his business card but denied any intention of using an inducement to obtain an interview. Knoll submitted that the use of gifts was a well established practice within the industry; the cost of which was defined by the Code. The representative stated that he had, on occasions, been requested by doctors' receptionists to write on his card what items he had available, although he did not recollect being asked to do so on this occasion. He denied ever leaving more than one gift with any one doctor.

Knoll stated that briefing material was only issued in respect of technical aspects of products, as required by Clause 15.9 of the Code. On appointment all representatives received a copy of the Code and the company's internal briefing document (SOP) which covered the application of the Code. The relevant section of the SOP stated "Representatives must not employ any inducement or subterfuge to obtain an interview". Knoll stated that representatives also received as part of their training a presentation on the Code from a member of the medical staff.

Knoll acknowledged that the note that the representative left could be misinterpreted and could be deemed inappropriate. The company had briefed its regional managers to ensure that a similar activity was avoided.

Knoll provided invoices for all of the items. The halogen lamp, branded with the product name "Protium", was intended for use within the surgery on the doctor's desk and cost £4.98 plus VAT. The unbranded storm umbrella was to protect the doctor and his equipment/bag from the rain when on home visits and cost £4.66 plus VAT. The medical instruments roll bag was branded with the product name "Protium" and was for minor surgical procedures. It cost £5 plus VAT.

### PANEL RULING

The Panel noted that Clause 15.3 of the Code stated that representatives must not employ any inducement or subterfuge to gain an interview. The Panel considered that the note written by the representative on his business card amounted to the representative offering the doctor inducements in order to gain an interview. A breach of Clause 15.3 was ruled.

During its consideration of this case the Panel noted that Clause 18.2 of the Code stated that gifts in the form of promotional aids might be distributed to members of the health professions provided that the gifts were inexpensive and relevant to the practice of the recipient's profession or employment. The supplementary information to Clause 18.2 stated that an inexpensive gift was one which had cost the donor company no more than £5 excluding VAT. The Panel noted from the invoices provided by Knoll that all of the gifts complied with the Code in terms of cost. The Panel noted that the gifts were being offered to a general practitioner and queried the relevance of a large umbrella to the practice of medicine. The Panel requested that this be drawn to Knoll's attention.

**Complaint received** **20 July 1998**

**Case completed** **29 September 1998**

CASE AUTH/747/7/98

# GENERAL PRACTITIONER v GOLDSHIELD

## Conduct of a representative

**A general practitioner complained that a Goldshield representative had offered to supply his practice with free hydroxocobalamin injections if he prescribed that company's brand of nifedipine.**

**The Panel noted that Goldshield had accepted that the offer made by its representative was unacceptable. It amounted to an inducement to prescribe and a breach of the Code was ruled. A further breach was ruled because the representative had failed to maintain a high standard of ethical conduct and comply with all of the relevant requirements of the Code. The Panel considered that the conduct of the representative had brought discredit upon, and reduced confidence in, the pharmaceutical industry and accordingly also ruled a breach of Clause 2 of the Code.**

### COMPLAINT

A general practitioner complained about the conduct of a representative from Goldshield Pharmaceuticals. In the course of a conversation the representative had offered to supply the practice with free hydroxocobalamin injections contingent on the complainant prescribing his company's brand of nifedipine. He repeated this offer in front of the practice manager. It was the complainant's understanding that this was contrary to Clause 18.1 of the Code.

### RESPONSE

Goldshield said that this was clearly a case of misconduct by the representative. He was not under any authorisation to offer inducements which, on this occasion, were free hydroxocobalamin injections. However, he was authorised to offer hydroxocobalamin injections for sale to the surgery at the approved retail price on direct delivery, subject to the practice requiring this product.

Any inducement to prescribe nifedipine was unauthorised and was a clear breach of conduct. The matter would be dealt with internally and under no circumstances would this reoccur. Unfortunately, despite a detailed briefing for the sale of hydroxocobalamin injections, this was clearly not actioned by this particular representative. Goldshield had no evidence of any such previous instances of misconduct by its representative. The representative had passed the ABPI Medical Representatives Examination in 1979.

### PANEL RULING

The Panel noted that Goldshield had accepted that the offer made by its representative was unacceptable. It amounted to an inducement to prescribe. A breach of Clause 18.1 was ruled. The Panel considered that the representative had failed to maintain a high standard of ethical conduct and comply with all the relevant requirements of the Code. The Panel ruled that there had been a breach of Clause 15.2 of the Code. The Panel also considered that the conduct of the representative brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

**Complaint received** **23 July 1998**

**Case completed** **12 August 1998**

CASE AUTH/749/7/98

# DIRECTOR v ORGANON

## Puregon advertisement

**Serono alleged that a journal advertisement for Puregon was in breach of an undertaking given by Organon in relation to a statement "A step-wise, gradually increasing dosage scheme is preferred, starting with 50IU/day of Puregon for 7 to 14 days". The Panel had considered that the statement was not a fair reflection of the information given in the summary of product characteristics (SPC) regarding the dose of Puregon (Case AUTH/645/11/97). The journal advertisement now at issue included the statement "Induction of ovulation has been shown to be satisfactory using starting doses of Puregon as low as 50IU".**

**As the Authority was responsible for ensuring compliance with undertakings, the matter was taken up as a complaint by the Director.**

**The Panel noted that the advertisement appeared in an international journal produced in English and published in the UK and considered that it was subject to the Code. The advertisement had been placed by the Dutch parent company, NV Organon, without the knowledge or approval of the UK based company. The Panel noted that if the overseas company was related to a UK based company, then the UK based company was held responsible. There was an element of inequity in this but it was necessary to take a pragmatic approach to the problem. This course of action had been used in previous cases.**

**The Panel considered, however, that given the origin of the advertisement it was inappropriate for Organon Laboratories in the UK to be ruled in breach of the Code for failing to comply with its undertaking. It nonetheless had to take responsibility for the advertisement.**

**The Panel decided that the advertisement was misleading as the statement "Induction of ovulation has been shown to be satisfactory using starting doses of Puregon as low as 50IU" was not a fair reflection of the dosage information in the SPC which recommended a sequential treatment scheme usually starting with daily administration of 75IU FSH activity. A breach of the Code was ruled.**

### COMPLAINT

Serono Laboratories (UK) Limited drew attention to an advertisement for Puregon which appeared in the May and June 1998 issues of Human Reproduction. Serono alleged that the advertisement was in breach of the undertaking and assurance given by Organon Laboratories Ltd in relation to a statement "A step-wise, gradually increasing dosage scheme is preferred, starting with 50IU/day of Puregon for 7 to 14 days" which the Panel had considered was not a fair reflection of the information given in the summary of product characteristics (SPC) regarding the dose of Puregon. The SPC stated that "In general a sequential treatment scheme is recommended starting with daily administration of 75IU". A breach of Clause 7.2 of the Code had been ruled. (Case AUTH/645/11/97).

In view of the fact that the complaint involved an alleged breach of undertaking, the matter was taken up as a complaint by the Director of the Authority as the Authority itself was responsible for ensuring compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

### RESPONSE

Organon Laboratories pointed out that the material at issue in Case AUTH/645/11/97 was a technical booklet for Puregon published by Organon Laboratories Ltd. The advertisement currently complained about was not placed by Organon Laboratories Ltd and therefore the company submitted that the undertaking had not been disregarded. The advertisement was placed without Organon Laboratories' prior knowledge, consent or approval, by the parent company NV Organon, the company registered in the Netherlands. The centralized marketing authorization for Puregon was held by NV Organon. Organon Laboratories pointed out that it was not customary for the parent company to seek approval for its actions from a local subsidiary.

In this instance the advertisement was placed for a product which was centrally approved in Europe and therefore did not hold a UK marketing authorization, the marketing authorization holder for which was not UK based and the advertisement appeared in an international journal which was an official publication of the European Society for Human Reproduction and Embryology (ESHRE). The journal was published by Oxford University Press.

It was not clear that Organon Laboratories should be held accountable for the actions of another independent organisation which was based outside, and operated outside the UK.

Organon Laboratories stated that it would appear that some of the circumstances in this case were similar to those in a recent case (AUTH/544/5/97) which referred to information on the Internet. In that case the Internet site had not been prepared by or supported with the knowledge of the UK companies and neither had they promoted the existence of the site. Organon Laboratories submitted that there were two similarities with the current complaint, the publication was not by a UK based company and the journal in which the advertisement was placed was available on the Internet. Organon Laboratories submitted that the latter fact was important as it was difficult to quantify the true circulation of the journal and, secondly, advertisements were not published on the Internet.

Organon Laboratories provided a copy of a checklist published by NV Organon to ensure worldwide compliance with the relevant national advertising standards. The very first element on the checklist was a commitment to compliance with the national codes and legislation of advertising. The present complaint had arisen out of a lack of appreciation that an advertisement

placed by NV Organon in an international journal could be subject to UK Code.

Organon Laboratories stated that the complaint raised a number of questions of responsibility. Firstly was it appropriate that the Authority had jurisdiction over advertising placed by non UK companies? Organon Laboratories was aware of a recent announcement by IFPMA that responsibilities for dealing with complaints should be with the national industry body if one existed and not with IFPMA. This was practical as monitoring of advertising in the UK must be ensured. The Authority should have jurisdiction over the person or company responsible for placing the advertisement. However the practicalities of dealing with companies which were not UK based and had not agreed to comply with the UK Code were real. Organon Laboratories questioned whether action was taken in respect of potential breaches of the Code against international companies with no UK based subsidiary. If the product were placed on the UK market by a non-UK based EC company what action could be taken against the company by the Authority in the event of perceived breaches of the UK Code. Organon Laboratories queried whether it was appropriate that UK based subsidiaries of international companies should be held responsible for the actions of another company. If the Authority accepted responsibility of monitoring of advertising placed by non UK and non ABPI member companies then Organon Laboratories should not be involved in the complaint.

Organon Laboratories submitted that natural justice would dictate that an individual company should only be held responsible for its own actions or for actions over which it exercised control. It should be recognised that a UK based company might have no control over advertisements placed by a second company, even although that second company was part of the same multinational or indeed was the parent organisation.

To conclude, Organon Laboratories submitted that it did not have any responsibility, legal or otherwise, in this particular instance. The Authority should not have jurisdiction in this particular case and it would be appropriate that complaints on advertising in an international form placed by an international organisation were dealt with by the IFPMA. Alternatively the complaint should be taken up in the Netherlands as that of the location of the company responsible for placing the advertisement. Nevertheless NV Organon had agreed that in future it would try to ensure that systems were in place which took account of local advertising requirements even when they placed advertising in international publications.

## PANEL RULING

The Panel noted that the Code applied to the promotion of medicines to members of the UK health professions and appropriate administrative staff. If the Code only covered advertising by UK companies as suggested by Organon Laboratories, then there would be a loop hole in that advertisements could be placed in the UK by companies outside the UK without any need to comply with the Code. Clearly this would be an untenable position. The Authority's position was that if the overseas company was related to a UK based company then the UK based company was held responsible under the Code. The Panel appreciated that there was an element of inequity in this but it was necessary to take a pragmatic approach to the problem. This course of action had been used in previous cases. One case (AUTH/215/9/94) had involved an advertisement placed by an overseas parent company in a European publication produced in the UK and circulated to UK health professionals. The subsidiary company in the UK had been ruled in breach of the Code. The question of jurisdiction had been appealed and the Appeal Board had upheld the Panel's ruling. The case had highlighted the need for companies to be aware of what their overseas parent companies were doing in the UK as the UK subsidiary would be responsible under the Code.

If there was no UK based company, a situation that had not arisen yet in a Code of Practice case although such advertisements had appeared in UK journals such as The Lancet and the British Medical Journal, then the matter would be taken up with the overseas company.

The Panel then turned to the case now before it.

The Panel first noted that the supplementary information to Clause 1.1 relating to journals with an international distribution stated that the UK Code applied to the advertising of medicines in professional journals which were produced in the UK and/or intended for a UK audience. The supplementary information further stated that international journals produced in English in the UK were subject to the Code even if only a small proportion of their circulation was to a UK audience.

The Panel noted that the journal in question was published in the UK and assumed that it would be circulated to UK health professionals. It was therefore subject to the UK Code.

The Panel did not accept Organon Laboratories' submission that the circumstances in this case were similar to those in a recent case concerning material on the Internet (Case AUTH/544/5/97). In that case the material had only appeared on the Internet and not in an advertisement to UK health professions in a journal produced in the UK and/or intended for a UK audience.

The Panel considered, however, that in the circumstances it was inappropriate for Organon Laboratories Ltd in the UK to be ruled in breach of the Code for failing to comply with its undertaking. It nonetheless had to take responsibility for the advertisement.

The Panel decided that the advertisement in question was misleading in that it included a statement that "Induction of ovulation has been shown to be satisfactory using starting doses of Puregon as low as 50IU". The statement was not a fair reflection of the information given in the SPC regarding the dose of Puregon that in general a sequential treatment scheme was recommended which usually started with daily administration of 75IU FSH activity. A breach of Clause 7.2 of the Code was ruled.

**Complaint received** **30 July 1998**

**Case completed** **18 September 1998**

CASE AUTH/758/8/98

# GLAXO WELLCOME v ZENECA PHARMA

## Zomig journal advertisement

**Glaxo Wellcome complained about an advertisement for Zomig issued by Zeneca Pharma. The advertisement was headed "WOW!" followed by the claim "In migraine Zomig 2.5mg is significantly more effective than sumatriptan 50mg for headache response at 2 and 4 hours". The data used to support the claim showed differences in headache response rate in favour of Zomig at 2 and 4 hours at 3% and 2% respectively. Glaxo Wellcome alleged that "WOW!" was a misleading exaggeration of what was a very small difference between the two products.**

**The Panel considered that the advertisement would give readers the impression that they would notice a large clinical difference between Zomig 2.5mg and sumatriptan 50mg. The Panel accepted that the data showed a statistically significant difference in favour of Zomig which might be clinically relevant but considered that, given its meaning, the use of the word 'WOW' in relation to the data was misleading. A breach of the Code was ruled.**

Glaxo Wellcome UK Limited complained about a journal advertisement for Zomig (zolmitriptan) (ref 98/9640) issued by Zeneca Pharma which appeared in Pulse, 18 July 1998. The advertisement was headed "WOW!" followed by "In migraine, Zomig 2.5mg is significantly more effective than sumatriptan 50mg for headache response at 2 and 4 hours".

### COMPLAINT

Glaxo Wellcome alleged that the advertisement was misleading in breach of Clause 7.2 of the Code.

The data on file used by Zeneca to support the claim of "WOW", showed that the response rates for zolmitriptan 2.5mg and sumatriptan 50mg at 2 hours and 4 hours were 67% vs 64% and 83% vs 81% respectively. GlaxoWellcome accepted the statistical analysis undertaken, but was surprised that such small differences (3% and 2%) could be significantly different. Glaxo Wellcome pointed out that the term "significance" had two meanings. The statistical sense, as in the data used to support this claim, but also the grammatical sense, meaning that something was of considerable importance.

Glaxo Wellcome alleged that the use of the word "WOW" and stating that zolmitriptan was significantly more effective than sumatriptan suggested to the reader that the difference between the two treatments was not only of statistical significance but also of real clinical importance. Glaxo Wellcome did not believe that a difference of 3% and 2% between these two treatments would be considered of real clinical importance to the reader. The only "WOW" that the advertisement brought to mind was how could such small differences be statistically significant!

In conclusion, Glaxo Wellcome alleged that "WOW" was a misleading exaggeration of response to what was, in fact, a very small difference between the two products.

### RESPONSE

Zeneca submitted that the Code required that promotional claims must be substantiated upon reasonable request to do so. There was no further requirement that such substantiation, in terms of actual response rates and 'p-values', be supplied along with the claim itself when it was made.

Zeneca did not consider that the claim "'Zomig' 2.5mg is significantly more effective than sumatriptan 50mg for headache response at 2 and 4 hours" was misleading as it was substantiated in the data on file by an odds ratio of 1.21 ($p = 0.017$) and an odds ratio of 1.23 ($p = 0.039$), for the two time points respectively. This was further supported by the fact that all the odds ratios reported in the study were greater than 1. Thus, given the greater likelihood of treatment success with Zomig 2.5mg versus sumatriptan 50mg, more migraineurs were likely to benefit from Zomig 2.5mg at 2 and 4 hours. Since migraine was so prevalent and was such a debilitating condition, the result was clinically meaningful and relevant as well as statistically significant.

Zeneca submitted that the odds ratios obtained and reported from the study were based on treatment of multiple headaches which represented a more clinically relevant measurement of successful treatment in a condition such as migraine, a chronic disorder with multiple, sometimes frequent, exacerbations. The purpose of measuring response to treatment in multiple attacks was to provide an assurance that the effect being measured was consistent and reliable over attacks for individual patients, and the results from this study had demonstrated this clinical value.

All of the end points in the study showed results better than, or at least as effective as sumatriptan (all the odds ratios were always greater than 1 but might not all be 'statistically significant'). Hence, overall clinically Zomig 2.5mg was better than sumatriptan 50mg.

Zeneca appreciated that it was a matter of clinical opinion, but did not agree with the contention that the overall differentials of 2% and 3% between Zomig and sumatriptan were not clinically meaningful.

Zeneca stated that it was well documented and acknowledged that sumatriptan was a highly effective product in its own right and thus any differential advantage could only be of a relatively small magnitude. Therefore, Zeneca did not consider it inappropriate to draw attention to the results being of considerable importance by the use of the word "WOW".

### PANEL RULING

The Panel noted that in the data on file supplied by Zeneca, Zomig 2.5mg had been compared with sumatriptan 50mg. These were the initial recommended

doses of both medicines. Headache response had been noted at 1, 2 and 4 hours. At 1 hour Zomig was at least as effective as sumatriptan (odds ratio ≥1) but at 2 and 4 hours it was significantly more effective ($p \leq 0.005$). Meaningful migraine relief had also been noted at 1, 2 and 4 hours. At 1 hour Zomig was at least as effective as sumatriptan (odds ratio ≥1), at 2 hours it was significantly better ($p \leq 0.01$) but at 4 hours it was again only at least as effective as sumatriptan (odds ratio ≥1). The Panel considered that there was a difference between clinical significance and statistical significance.

The Panel noted that the word "WOW" was defined as an exclamation of admiration, amazement, a person or thing that was amazingly successful, or attractive.

The Panel considered that the advertisement would give readers the impression that they would notice a large clinical difference between Zomig 2.5mg and sumatriptan 50mg. The Panel accepted that the data showed a statistically significant difference in favour of Zomig 2.5mg for headache response at 2 and 4 hours and this might be clinically relevant. The Panel considered, however, that given its meaning, the use of the word "WOW" in relation to the data presented was misleading. A breach of Clause 7.2 of the Code was ruled.

**Complaint received** **19 August 1998**

**Case completed** **1 October 1998**

---

**CASE AUTH/760/8/98** *NO BREACH OF THE CODE*

# RHÔNE-POULENC RORER v PHARMACIA & UPJOHN

## Fragmin journal advertisement

**Rhône-Poulenc Rorer complained about an advertisement for Fragmin issued by Pharmacia & Upjohn. The main theme of the advertisement was the convenience of Fragmin but the following claim regarding efficacy was included "Reduces cardiovascular morbidity and mortality in UCAD [unstable coronary artery disease] by up to 63% (p = 0.001)." The claim was referenced to the FRISC study.**

**The Panel did not consider that the claim was a hanging comparative as alleged. Given the theme of the advertisement and the fact that there was no mention of the efficacy of Fragmin in comparison with other agents, the claim would be taken to be versus placebo which was the case. No breach of the Code was ruled.**

Rhône-Poulenc Rorer Limited complained about a journal advertisement for Fragmin (Ref: P3525) which had been issued by Pharmacia & Upjohn Limited. The advertisement carried the headline "Adds convenience to your control of unstable coronary artery disease" and featured a photograph of a shattered glass of red wine. Beneath the visual were three bullet points regarding the convenience, cost and efficacy of Fragmin.

### COMPLAINT

Rhône-Poulenc Rorer alleged that the third bullet point "Reduces cardiovascular morbidity and mortality in UCAD [unstable coronary artery disease] by up to 63% (p=0.001)", which was referenced to the FRISC study, was a hanging comparative in breach of Clause 7.2 of the Code.

Rhône-Poulenc Rorer drew attention to intercompany correspondence on the matter in which Pharmacia & Upjohn had written "[The claim] does not state that Fragmin is 'better' or 'stronger' without the use of a comparator but is a statement of efficacy (against placebo) in a clearly referenced study". Rhône-Poulenc Rorer noted that the words "against placebo" had to be included as it was not clear from the piece as it required detailed knowledge of the FRISC study which was only referenced in superscript as reference 1.

### RESPONSE

Pharmacia & Upjohn did not accept that its advertisement was in breach of Clause 7.2 of the Code. The company noted that Clause 7.2 warned against the use of statements involving hanging comparisons. The examples in the supplementary information included the adjectives 'better', 'stronger' etc, the question 'better/stronger than what?' being implicit in the statement. Pharmacia & Upjohn stated that the claim that Fragmin "Reduces cardiovascular morbidity and mortality in UCAD by up to 63% (p=0.001)" did not use any such adjective and was a clearly referenced statement of fact.

Pharmacia & Upjohn stated that the argument that the customer would need a detailed knowledge of the FRISC study to interpret the statement did not hold water since the reference was available on request. The reason all claims in any promotional material were referenced was that the customer could not possibly have a detailed knowledge of all papers but could request them in order to ensure that the claim was substantiable.

### PANEL RULING

The Panel noted that the main theme of the advertisement was the convenience of Fragmin; it could be administered in a convenient regimen by a simple sub-cutaneous injection, was not as complicated to administer as standard heparin and patients did not require monitoring. The claim in question addressed the efficacy of Fragmin. The Panel considered that, given the theme of the advertisement and the fact that there was no mention of the efficacy of Fragmin in comparison with other agents, the claim would be taken to be versus placebo which was the case. No breach of Clause 7.2 was ruled.

**Complaint received** **24 August 1998**

**Case completed** **7 October 1998**

CASE AUTH/761/8/98

# SETON HEALTHCARE v SMITH & NEPHEW

## Promotion of Iodosorb and Iodoflex

**Seton Healthcare complained about a promotional scheme for Iodoflex and Iodosorb run by Smith & Nephew Healthcare Limited. Details of the scheme were given on an A4 piece of paper which stated "Save 40 Intrasite Gel caps and 2 Iodoflex/Iodosorb cartons." Iodoflex and Iodosorb were both licensed medicines Seton stated that in return for the items of packaging collected, healthcare professionals would receive a watch. Smith & Nephew stated that the watch was valued at £5 and was a promotional aid given as a gift.**

**The Panel considered that it was a clearly established principle that no gift, benefit in kind or pecuniary advantage should be offered or given as an inducement to prescribe, supply, administer or buy any medicine. In the Panel's view this also meant that a promotional aid could not be used as an inducement. The Panel considered that it was inappropriate to link the supply of a promotional aid to the use of a medicine by collecting packaging.**

**The involvement of Iodoflex and Iodosorb brought the scheme within the scope of the Code. The Panel considered that the watch was not unacceptable as a promotional aid and ruled no breach of the Code in that regard. It had, however, been used as an inducement and a breach of the Code was ruled.**

**The Panel considered that the A4 piece of paper was promotional and so it should have included prescribing information for the medicines to which it referred. A breach of the Code was ruled. Overall the Panel considered that the scheme was in breach of the Code as it had failed to maintain a high standard.**

### COMPLAINT

Seton Healthcare plc complained about a promotional scheme for Iodoflex and Iodosorb run by Smith & Nephew Healthcare Limited.

The details about the scheme were given on a A4 piece of paper which stated "Save 40 Intrasite Gel caps and 2 Iodoflex/Iodosorb cartons. Offer ends 31 December 1998. See your Smith & Nephew salesperson for details"

Seton stated that healthcare professionals were invited to contact their local Smith & Nephew salesperson and in return for items of packaging collected they would receive a watch.

Seton had contacted Smith & Nephew about the matter, pointing out that Iodoflex and Iodosorb were both licensed medicines. Smith & Nephew had indicated that the promotion had been amended to include only Intrasite Gel and that a letter had been sent to the healthcare professionals taking part, advising them of the change. Seton was concerned that, contrary to initial discussions, a breach of the Code was now being denied and the covering letter sent to participants did not advise them fully of the reasons for the change.

Seton alleged that the promotion was in breach of the Code for six reasons: -

1 Clause 2 – The promotion clearly brought discredit upon and reduced confidence in the pharmaceutical industry.

2 Clause 4.1 – The A4 sheet giving details about the scheme should have included prescribing information.

3 Clause 9.1 – The material and activity did not recognise the special nature of medicines and caused offence. The promotion was certainly not of a "high standard" as demanded by this clause.

4 Clause 15.2 – As representatives were key to the communication process there was a breach of this clause.

5 Clause 18.1 – The promotion was an inducement to prescribe and administer a medicine.

6 Clause 18.2 – A watch with a value to Smith & Nephew of less than £5 would not be of relevance to the work of the healthcare professional. If it was intended that the watch was a prize and therefore should have a value of less than £100, such a competition would not meet the requirements of Clause 18.2 in terms of it being a *bona fide* test of skill recognising the professional standing of the recipients.

As indicated to Smith & Nephew, Seton was surprised that this activity was similar to one involving another Smith & Nephew product where a breach of the Code had been ruled (Case AUTH/188/7/94)

### RESPONSE

Smith & Nephew confirmed that it had been in correspondence with Seton about this matter. It had not accepted that a breach of the Code had occurred. Smith & Nephew had decided that it would be in the best interests of the industry, and its relationship with Seton, to modify the campaign in an attempt to engender a spirit of co-operation between the companies.

The promotion was aimed at healthcare professionals who routinely dealt with high exudating sloughy wounds. It was intended that it would position two of the company's new products alongside its well established product, Intrasite Gel. The promotion was in the form of the participants collecting a number of pack tops of the three products they would normally use, sending them to the company in exchange for a gift of a watch. At no time was it used as an inducement to order material above that which they would normally use in the course of their work.

Smith & Nephew submitted that, in essence, it did not believe that this activity contravened Clause 18.1 as the watch in question was a promotional item and valued at £5. As a promotional item a watch satisfied the requirements of Clause 18.2 in that it fell into the same category as pens, diaries, desk clocks and calendars, all of which had been deemed acceptable within the Code. As everyone was now under considerable time constraints

and the need to meet rigorous schedules, a watch was very relevant to the way in which healthcare professionals performed their daily work. The company drew a direct comparison between a desk clock for a surgery and a watch used by district nurses who travelled between patients.

Smith & Nephew submitted that it had amended the promotion to focus on Intrasite Gel as it did not want to disadvantage those people already participating.

Smith & Nephew responded to the points made by Seton as follows:

1 The promotion did not discredit nor reduce confidence in the pharmaceutical industry as the promotion had been professionally managed and the gift was of a quality associated with the pharmaceutical industry.

2 The promotion was detailed on an A4 sheet and only involved the name of the medicine and did not include any product claims. It was a factual announcement of the promotion and as such, it was not included within the Code.

3 The promotion had been carried out in the spirit of the Code and had not caused any offence to the recipients. It was difficult to gauge if a promotion caused offence but the company had received no adverse comments from any source except Seton Healthcare and there were 600 participants in the scheme.

4 The role of the representative was purely one of explaining the promotion to the recipient, at no time did they use this promotion for the purpose of gaining access to the healthcare professional nor did they use this promotion to directly gain orders for the items detailed in the promotion.

5 Smith & Nephew did not believe that this promotion would induce any healthcare professional to purchase any more of the products than they would normally do so in the routine course of their work. The aim of the promotion was to ensure the correct positioning of the new products in the treatment of high exudating sloughy wounds, not one which was directly connected to the receipt of orders.

6 The watch in question was valued at £5 and hence within the Code. It was not intended as a competition prize but as a promotional aid given as a gift.

Smith & Nephew referred to a previous case, Case AUTH/188/7/94, regarding its campaign involving Bactigras which offered district nurses the chance to earn medical instruments and accessories by collecting points. A breach of Clause 18.1 had been ruled as the offer was directly linked to sales of the product. Smith & Nephew agreed with the ruling given at that time. It did not believe the two promotions were comparable. The Bactigras promotion was aimed at increasing sales and the prizes were graded as to the quantity of product purchased ie the more product purchased, the larger the prize. The current promotion was aimed at positioning the product and there was only one gift available, the value of which was within the Code.

## PANEL RULING

The Panel noted that the promotional scheme at issue was different to the Bactigras scheme which had been ruled in breach of the Code (Case AUTH/188/7/94). Under the current scheme the healthcare professional was given a gift costing £5 whereas Case AUTH/188/7/94 had involved more expensive items.

The Panel noted that Clause 18.2 allowed companies to give promotional aids to health professionals and others, provided they cost the donor company no more than £5 excluding VAT, and were relevant to the recipient's profession or employment.

The Panel considered that it was a clearly established principle that no gift, benefit in kind or pecuniary advantage should be offered or given as an inducement to prescribe, supply, administer or buy any medicine subject to the provisions of Clause 18.2 of the Code. In the Panel's view, this also meant that a promotional aid could not be used as an inducement. A promotional aid which met the requirements of the Code could of course be given to a healthcare professional but the Panel considered that it was inappropriate to link its supply to the use of a medicine by collecting packaging as had been done by Smith & Nephew.

In the original promotion, healthcare professionals would only receive a watch if they had collected 2 Iodoflex/Iodosorb cartons as well as 40 caps from Intrasite Gel. Intrasite Gel was not a licensed medicine and only the involvement of Iodoflex and Iodosorb brought the scheme within the scope of the Code. The Panel considered that the promotional aid had been used as an inducement contrary to the requirements of Clause 18.1 of the Code and a breach of that Clause was ruled.

The Panel had reservations about the acceptability of a watch as a promotional aid. It considered that on balance the watch in question was not unacceptable as a promotional aid. It was no less relevant than a desk clock which was specifically mentioned in the supplementary information to Clause 18.2 as being allowed. No breach of Clause 18.2 was ruled.

The Panel did not accept that the A4 piece of paper giving details of the promotion was within the exemption to the definition of promotion for factual, accurate, informative announcements and reference material relating, for example, to pack changes, adverse reaction warnings, trade catalogues and price lists. The message was a promotional one. It was therefore subject to the Code and should have included prescribing information for the medicines to which it referred. A breach of Clause 4.1 of the Code was ruled.

The Panel considered that the scheme was inappropriate and failed to maintain a high standard. The Panel therefore ruled a breach of Clause 9.1 of the Code.

The Panel considered that the matter was not one that warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure. The Panel did not consider that there was a breach of Clause 15.2. The matter was adequately covered by the ruling of a breach of Clause 18.1.

**Complaint received** **28 August 1998**

**Case completed** **15 October 1998**

# CODE OF PRACTICE REVIEW - NOVEMBER 1998

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

| | | | | | |
|---|---|---|---|---|---|
| **677/2/98** | **Wyeth v Astra** | **Losec detail aid** | **Breach 7.2, 7.6 & 8.1** | **Appeal by respondent** | **Page 5** |
| **681/2/98 & 682/2/98** | **Amgen v Chugai and Rhône-Poulenc Rorer** | **Granocyte detail aid** | **Breach 7.2** | **Appeal by respondents** | **Page 22** |
| **687/3/98** | **Schwarz Pharma v Astra** | **MUSE formulary pack** | **Breach 7.2** | **No appeal** | **Page 36** |
| **693/4/98** | **Consultant Cardiologist v Roche** | **Posicor mailing** | **Breach 7.2** | **Appeal by complainant** | **Page 40** |
| **694/4/98** | **Glaxo Wellcome v Astra** | **Oxis Turbohaler 12 leavepieces** | **Breach 7.2** | **No appeal** | **Page 42** |
| **695/4/98 & 696/4/98** | **Consultant Physician v Janssen-Cilag and Organon** | **Risperdal mailing offer** | **Breach 15.3** | **Appeal by respondents** | **Page 44** |
| **699/4/98** | **Organon v Serono** | **Gonal-F detail aid** | **Breach 7.2 & 7.6** | **No appeal** | **Page 46** |
| 702/4/98 | Director/Media v Biogen | Media lunch | No breach | No appeal | Page 49 |
| **703/5/98** | **Glaxo Wellcome v Merck Sharp & Dohme** | **Singulair detail aid** | **Breach 7.6** | **Appeal by complainant** | **Page 50** |
| 704/5/98 | Hospital Pharmacist v Leo | Innohep advertisement | No breach | No appeal | Page 53 |
| 705/5/98 | Practice Services Manager v Trinity | Conduct of representative | No breach | No appeal | Page 54 |
| **707/5/98** | **Director of Pharmacy Services v Knoll** | **Conduct of representative** | **Breach 15.2** | **No appeal** | **Page 56** |
| 708/5/98 | General Practitioner v Merck Sharp & Dohme | Innovace Melt mailing | No breach | No appeal | Page 57 |
| **709/5/98** | **Director v Schering-Plough** | **Failure to comply with undertaking** | **Breach 2 & 21 Obligatory audit** | **Appeal by respondent** | **Page 58** |
| **710/5/98** | **Glaxo Wellcome v Merck Sharp & Dohme** | **Singulair advertisement on MIMS** | **Breach 4.1** | **No appeal** | **Page 61** |
| **712/5/98** | **Hoechst Marion Roussel Nurse Advisor v Hoechst Marion Roussel** | **Conduct of representative** | **Breach 9.1 & 15.2** | **No appeal** | **Page 62** |
| **713/5/98** | **Whitehall v Searle** | **Powergel advertisement** | **Breach 7.2** | **No appeal** | **Page 65** |
| **714/5/98 & 725/6/98** | **Chugai Pharma v Amgen and Roche** | **Neupogen Syringe detail aid** | **Breach 7.2** | **No appeal** | **Page 67** |
| **717/6/98** | **General Practitioner v Lilly** | **Distaclor MR mailing** | **Breach 7.2** | **No appeal** | **Page 71** |
| **718/6/98** | **Allergan v Pharmacia & Upjohn** | **Xalatan brochure** | **Breach 7.2 & 7.6** | **No appeal** | **Page 72** |
| **719/6/98** | **Schering-Plough v UCB Pharma** | **Promotion of Zirtek** | **Breach 15.2 & 15.9** | **No appeal** | **Page 76** |
| **720/6/98** | **Former Health Service Manager v Boehringer Ingelheim** | **Oramorph advertisement in Health Service Journal** | **Breach 12.1** | **No appeal** | **Page 78** |
| **721/6/98** | **Hospital Pharmacist v Servier** | **Highlights From... The European Cardiologist Journal by Fax** | **Breach 10.1** | **No appeal** | **Page 79** |
| **722/6/98** | **General Practitioner v Astra** | **Imdur mailing** | **Breach 7.2** | **No appeal** | **Page 80** |

| | | | | | |
|---|---|---|---|---|---|
| **723/6/98** | **Hoechst Marion Roussel v UCB Pharma** | **Promotion of Zirtek** | **Breach 7.2, 7.3, 7.8 & 8.1** | **No appeal** | **Page 82** |
| **724/6/98** | **Glaxo Wellcome v Merck Sharp & Dohme** | **Information on montelukast in Pharmatrak** | **Breach 7.2** | **No appeal** | **Page 86** |
| 726/6/98 | Merck Sharp & Dohme v Glaxo Wellcome | Serevent advertisements | No breach | Appeal by respondent | Page 88 |
| 727/6/98 | Diabetes Charity v Lilly | Humalog advertisement | No breach | No appeal | Page 90 |
| 729/6/98 | Former Health Service Manager v Merck Sharp & Dohme | Zocor advertisement in Health Service Journal | No breach | No appeal | Page 92 |
| **730/6/98** | **Former Health Service Manager v Hoechst Marion Roussel** | **Telfast 120 advertisement in Health Service Journal** | **Breach 12.1** | **No appeal** | **Page 94** |
| **731/6/98** | **Dermal v Goldshield** | **Promotion of Fenbid** | **Breach 4.1, 7.2, 7.6 & 7.10** | **No appeal** | **Page 95** |
| **732/6/98** | **Director/Paragraph 16 v Schering-Plough** | **Sponsorship of medical dinner dance** | **Breach 19.1** | **No appeal** | **Page 97** |
| **733/6/98** | **Consultant Haematologist v Wyeth** | **Zoton advertisements** | **Breach 9.2** | **No appeal** | **Page 98** |
| 734/6/98 | Director/Media v Roche | Promotion of Posicor | No breach | No appeal | Page 99 |
| **735/7/98 & 736/7/98** | **Merck Sharp & Dohme v Parke Davis and Pfizer** | **Promotion of Lipitor** | **Breach 7.2** | **Appeal by respondents** | **Page 101** |
| **737/7/98** | **Former Health Service Manager v Merck Sharp & Dohme** | **Advertisement for Singulair in NHS Confederation Commemorative Diary** | **Breach 12.1** | **No appeal** | **Page 106** |
| 738/7/98 | Former Health Service Manager v BSIA | Advertisement for Pylobactell in Healthcare today | No breach | No appeal | Page 107 |
| **739/7/98** | **General Practitioner v Bayer** | **Promotion of Ciproxin** | **Breach 7.2** | **Appeal by respondent** | **Page 109** |
| **740/7/98** | **General Practitioner v Astra** | **Losec advertisement** | **Breach 7.2 & 7.8** | **No appeal** | **Page 111** |
| 742/7/98 | General Practitioner v Schering-Plough | Sampling of Elocon | No breach | No appeal | Page 113 |
| **743/7/98** | **Former Health Service Manager v Merck Sharp & Dohme** | **Advertisement for Singulair in NHS conference papers** | **Breach 12.1** | **No appeal** | **Page 114** |
| **746/7/98** | **General Practitioner v Knoll** | **Conduct of representative** | **Breach 15.3** | **No appeal** | **Page 116** |
| **747/7/98** | **General Practitioner v Goldshield** | **Conduct of representative** | **Breach 2, 15.2 & 18.1** | **No appeal** | **Page 117** |
| **749/7/98** | **Director v Organon** | **Puregon advertisement** | **Breach 7.2** | **No appeal** | **Page 118** |
| **758/8/98** | **Glaxo Wellcome v Zeneca** | **Zomig advertisement** | **Breach 7.2** | **No appeal** | **Page 120** |
| 760/8/98 | Rhône-Poulenc Rorer v Pharmacia & Upjohn | Fragmin advertisement | No breach | No appeal | Page 121 |
| **761/8/98** | **Seton Healthcare v Smith & Nephew** | **Promotion of Iodoflex and Iodosorb** | **Breach 4.1, 9.1 & 18.1** | **No appeal** | **Page 122** |

# PRESCRIPTION MEDICINES
# CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, more than fifty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings including payment of travelling and accommodation expenses in connection therewith
- the provision of information to the general public either directly or indirectly
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Philip Cox QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 0171-930 9677 facsimile 0171-930 4554).