PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 50 NOVEMBER 2005

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.

Updated Code of Practice agreed by ABPI members

At the Half-Yearly General Meeting of The Association of the British Pharmaceutical Industry (ABPI) on 3 November, member companies agreed a revised version of the Code of Practice for the Pharmaceutical Industry. The new Code will come into operation on 1 January 2006 but, during the period 1 January to 30 April inclusive, no promotional material or activity will be regarded as being in breach of the Code if it fails to comply with its provisions only because of requirements newly introduced.

Also agreed was a revised version of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority. This also comes into operation on 1 January but certain aspects will apply only to complaints received on and after 1 January.

The main changes to the Code and the Constitution and Procedure are set out below. Full details have been sent to the chief executives of ABPI member companies and those companies which, though not ABPI members, have agreed to comply with the Code and accept the jurisdiction of the Authority.

Printed copies of the new Code are now available and a copy has been sent to everyone on the mailing list for the Code of Practice Review. Bulk orders from companies will be dispatched as soon as possible.

Changes to the Code of Practice

The following are the main changes to the Code:

General
References to doctors are changed where appropriate to prescribers or similar.

Clause 1
The Code will apply to information to the public about prescription only medicines and not as currently to information about medicines. More guidance about European/international events is included.

Clause 4 and Clause 5
There is now a requirement to refer readers to the SPC for side effects not mentioned in the advertising and a requirement to include in promotional material information on reporting adverse events.

Clause 6
The number of pages bearing advertising is limited to two per product per issue of a journal.

Clause 7
Rational use of a medicine must be encouraged by presenting it objectively and without exaggerating its properties.

It will be a breach of the Code to make reference to a clinical trial that is required to be registered in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases but which has not been so registered.

Clause 12
Deleted from the supplementary information 'Frequency of Mailings' is that 'A higher frequency rate will be accepted for mailings on new products than for others'. Limits on the number of mailings for a medicine of 8 per year and 4 in the first six months following launch of a medicine (excluding mailings solely about safety issues) are introduced.

Clause 14
Pharmacists are now allowed to certify certain promotional material in place of a medical practitioner. Additional guidance about qualifications for signatories is included. Educational materials for the public or patients issued by companies which relates to diseases or medicines including material related to working with patient organisations are to be certified. Certain materials relating to the provision of medical and educational goods and services are to be certified.

Clause 16
Representatives are required to enter the examination within their first year of commencing such employment. Exemptions to the examination are deleted. Personnel are required to be fully conversant with pharmacovigilance requirements relevant to their work.

Clause 18
Competitions and quizzes no longer permitted. More advice about appropriate promotional aids (cost to stay at £6 plus VAT). Guidance about switch and therapy review programmes has been added.

Clause 19
There is more guidance about hospitality, use of the term subsistence. Companies are to provide only economy airfares to delegates sponsored to attend meetings. More guidance about venues, more requirements for justifying holding meetings outside the UK. Clause 19 now applies to meetings of patients, patient groups and journalists.

Clause 20
Amended to apply solely to prescription only medicines. More detail about what information can be provided to the public is included. Requirements introduced regarding transparency of interactions with patient organisations.

Clause 21
Amended in relation to what can be accessed by the public on company websites.

Changes to the Constitution and Procedure

The following are the main changes to the Constitution and Procedure:

Paragraph 3
Vacancies for independent members of the Code of Practice Appeal Board (other than the Chairman) are to be advertised in the professional/national press.

There are to be two additional independent members for the Appeal Board, an independent registered nurse prescriber and a lay representative

Paragraph 7
Following a Panel ruling the time periods for comments are to be decreased from ten working days to five working days so that cases for appeal are dealt with more quickly.

The Panel is to have the power to require suspension of material/activities ruled in breach in certain circumstances, pending the outcome of an appeal.

Paragraph 10
Pre-vetting to be introduced as a sanction after a company has been audited. The Appeal Board is to have additional sanctions (public reprimand and corrective statements).

Paragraph 13
Brief details of companies ruled in breach of Clause 2 or required to issue a corrective statement or the subject of a public reprimand are to be advertised in the medical/pharmaceutical press. Case reports are to be published more frequently on the PMCPA website. PMCPA website will also include brief details of ongoing cases.

Paragraph 18
There will be increased scrutiny of material, including meetings.

OTHER MATTERS
There will be more resources for the PMCPA including additional staff. Increases to the levy, administrative charges and charges for audits. There will be increased communication to the NHS about the Code. The Guide to the Code for health professionals will be updated. A Guide to the Code for the public, patients and patient organisations will be produced.

CODE OF PRACTICE TRAINING

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

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

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

Thursday, 12 January

Thursday, 9 February

Friday, 10 March

Short training sessions on the Code or full all day seminars can be arranged for individual companies, including advertising and public relations agencies and member and non member companies of the ABPI. Training sessions can be tailored to the requirements of the individual company.

For further information regarding any of the above, please contact Jean Rollingson for details (020 7930 9677 extn 4).

How to contact the Authority

Our address is:

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

www.pmcpa.org.uk

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7930 9677 extn 5).

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

Heather Simmonds:	020 7747 1438
Etta Logan:	020 7747 1405
Jane Landles:	020 7747 1415

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

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

CASE AUTH/1603/7/04

AVENTIS PHARMA v NOVO NORDISK

Hospitality at meetings

Aventis Pharma complained about two meetings arranged by Novo Nordisk. Both invitations were headed 'insulin detemir invitation to information session', one taking place on 18 June 2004 and the other on 21 June 2004.

A range of health professionals including physicians, diabetes specialist nurses and dieticians were invited to the meeting which took place on 18 June 2004. Aventis alleged that the hospitality associated with this meeting was out of proportion to its scientific content. The arrangements were that the meeting took place on a floating restaurant; guests were welcomed with champagne and canapés between 7pm and 8pm; three presentations were given lasting one hour in total which addressed various aspects of Levemir; a buffet meal and drinks were provided following the presentations and live music; dancing and an open bar were subsequently provided.

The invitation to the second meeting on 21 June 2004 invited health professionals to watch a televised football match between England and Croatia as part of the meeting. The arrangements for the associated hospitality were unbalanced and were: drinks and canapés were offered from 5.30pm; a presentation summarising the major Levemir clinical studies was scheduled between 6pm and 7pm; a buffet and drinks were to be served at 7pm; at 7.45pm attendees were invited to watch the football match and the invitation specifically stated that the bar would remain open during the match.

The football match lasted ninety minutes, whilst the scientific presentations lasted one hour. In this invitation, the emphasis placed on the football, together with the food and beverages available, clearly indicated that the offer of hospitality was out of proportion to the scientific content of the meeting.

The Panel considered each meeting separately. The invitation to the meeting on the floating restaurant stated that guests would be welcomed from 7pm onwards by a reception drink, followed by a presentation summarising the major Levemir clinical studies. A barbecue would be available from 8.45pm onwards. There was no mention on the invitation as to who the speakers would be; it appeared that there would be only one presentation. The letter referred to 'the panel' being available during the evening to answer any questions about Levemir. The identity of the panel was not given but readers might have assumed that it consisted of the three people whose names appeared at the bottom of the letter; Novo Nordisk's medical manager and two sales managers.

In the Panel's view invitees would assume, given the wording of the invitation, that the educational part of the evening would last from approximately 7.30pm-8.45pm. The Panel noted Novo Nordisk's submission that the presentations had in fact lasted from 7.35pm to 9.15pm ie an hour and forty minutes.

The Panel noted that the final bill for the evening was £11,020.63 for 95 attendees. The cost per head was thus £116 which included payment for four musicians (£1,000) and two samba dancers (£700). The Panel noted that the evening had started with champagne and canapés.

The Panel considered that the arrangements for the meeting were unacceptable. The hospitality provided was out of proportion to the occasion and, in the Panel's view, the cost was more than the recipients would normally adopt when paying for themselves. Delegates would be attracted to the meeting because of the venue and the hospitality, not because of the programme. The impression created by the arrangements was important. A breach of the Code was ruled.

With regard to the second meeting at issue, the Panel noted that the letter of invitation highlighted the following in red type: 'The Executive Suite of [a named local football] Venue ….; 5.30pm; midsummer buffet dinner & drinks … 7.00pm … 7.45pm … Euro 2004 with the England v Croatia football game; Please confirm your attendance'. The Panel considered that the invitation was such that it sought to attract attendees to the meeting by virtue of the venue and the associated hospitality and not the educational content.

The Panel noted that the invitation to the meeting stated that delegates would be welcomed from 5.30pm onwards with a reception drink and canapés. There would then be a presentation on Levemir before a buffet dinner was served at 7pm followed by the football match, viewed on a plasma screen, at 7.45pm. The bar was to remain open during the match. In the Panel's view invitees would assume that the education part of the meeting would last no more than an hour.

The Panel noted that the total cost of the meeting was £1,452.53 (including VAT). The invoice indicated that there were 32 delegates; the cost per head was thus £45.39. The Panel noted that the meeting had started with champagne and canapés.

The Panel considered that the arrangements for the meeting were unacceptable. The hospitality provided was out of proportion to the occasion. In the Panel's view the evening was primarily a social and sporting event. The meeting appeared to have been arranged around a scheduled England football game. The impression created by the arrangements was important. A breach of the Code was ruled.

Overall the Panel was extremely concerned about the arrangements for the meetings. Although Novo Nordisk had submitted that core programmes had been agreed centrally, local representatives had been able to adapt these for their own needs but such modifications had been agreed with Novo Nordisk's medical department. The two letters of invitation bore reference numbers suggesting that they had been approved under the Code. The Panel noted that it could not make any ruling under Clause 2 of the Code as no allegation of a breach of that clause had been alleged. Given the circumstances the

Panel considered that had such an allegation been made it would have ruled a breach of Clause 2 as a sign of particular censure. The Panel decided to report Novo Nordisk to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board was extremely concerned about the arrangements for the two meetings; the impression created was unacceptable. Delegates would not be primarily attracted by the programme but by the associated hospitality. The Appeal Board also noted fundamental errors in the content of the letter template provided to the representatives. There appeared to be a lack of understanding of the requirements of the Code at head office level. The Appeal Board decided that, in accordance with Paragraph 10.4 of the Constitution and Procedure, Novo Nordisk should be required to undergo an audit of its procedures relating to the Code. Following receipt of the audit report, the Appeal Board would then consider whether further action was necessary.

Upon receipt of the audit report the Appeal Board decided that the company should be re-audited the next month.

Upon receipt of the report on the follow-up audit, the Appeal Board noted that progress had been made. It was concerned that there was no representatives' briefing material for Kliovance, Levemir or Novo Seven. Novo Nordisk stated that this would be available by its May sales conference. The Appeal Board noted the recommendation from the audit report, that representatives must be given written instructions on the application of the Code.

The Appeal Board decided to adjourn its consideration of the audit report in order for Novo Nordisk to provide the Authority with copies of the representatives' briefing material and assurances with regard to the recommendation noted above. Following assessment by the Authority of these items and resubmission of the revised Novo Seven representatives' briefing material, the Appeal Board decided that no further action was required.

Aventis Pharma Ltd complained about two meetings arranged by Novo Nordisk Limited. Both invitations were headed 'insulin detemir invitation to information session', one taking place on 18 June 2004 at a restaurant and the other on 21 June 2004 at a football club venue. Insulin detemir was marketed as Levemir by Novo Nordisk. Aventis supplied Lantus (insulin glargine).

COMPLAINT

Aventis Pharma provided a copy of the invitation to the meeting which took place on 18 June 2004. A range of health professionals including physicians, diabetes specialist nurses and dieticians were invited. Aventis alleged that the hospitality associated with this meeting was out of proportion to its scientific content, in breach of Clause 19.1. The arrangements were:

- the meeting took place in a restaurant;
- guests were welcomed with champagne and canapés between 7pm and 8pm;
- three presentations were given lasting one hour in total – these addressed various aspects of Levemir; a doctor from the Novo Nordisk medical department gave one of these presentations;
- a buffet meal and drinks were provided following the presentations, and
- live music, dancing and an open bar were subsequently provided.

The invitation to the second meeting on 21 June 2004 invited health professionals to watch a televised football match between England and Croatia as part of the meeting. The arrangements for the associated hospitality were again unbalanced and were:

- drinks and canapés were offered from 5.30pm;
- a presentation summarising the major Levemir clinical studies was scheduled between 6pm and 7pm;
- a buffet and drinks were to be served at 7pm;
- at 7.45pm attendees were invited to watch the football match, and
- the invitation specifically stated that the bar would remain open during the match.

The football match lasted ninety minutes, whilst the scientific presentations lasted one hour. Clause 19.1 stipulated that meetings which were mainly of a sporting nature were unacceptable and that hospitality must be secondary to the purpose of the meeting. In this invitation, the emphasis placed on the football coverage, together with the food and beverages available, clearly indicated that the offer of hospitality was out of proportion to the scientific content of the meeting. Aventis therefore alleged that this meeting too, was in breach of Clause 19.1.

Aventis stated that on 19 February 2004 it initiated a meeting with Novo Nordisk to highlight two concerns regarding its promotion of Levemir. Firstly, that it had evidence that Levemir was being promoted in advance of receipt of its marketing authorization; a number of methods were being utilised, including meetings with a broad range of health professionals. Secondly, that the level of hospitality indicated in the invitations at such meetings was clearly out of proportion to their advertised educational content. Aventis' concerns were discussed and Novo Nordisk agreed to withdraw a CD ROM containing promotional information about Levemir. It was also agreed that care would be taken to ensure that after the marketing authorization was received, all future promotional meetings should comply with the requirements of the Code. In order to ensure that this was the case, Novo Nordisk stated that its medical department approved each promotional meeting in advance, giving due consideration to the meeting topic, venue, costs and honoraria.

Having become aware of the two meetings above, Aventis wrote to Novo Nordisk's Managing Director – Vice President Europe, to ensure that senior management at Novo Nordisk endorsed the recent meetings programme. The reply confirmed that this was the case.

Aventis concluded from Novo Nordisk's agreement that elements of the meetings programme pre-

marketing Levemir appeared to be inappropriate and from the two meetings cited above, that the governance of promotional meetings at Novo Nordisk was inadequate and woefully below the acceptable industry standard.

RESPONSE

Novo Nordisk stated that the EU Commission made its final decision on the marketing authorization for Levemir on 1 June 2004. This marked the date from which Levemir could be promoted throughout the EU countries.

Novo Nordisk planned the Levemir information sessions at headquarters level and drafted a generic programme and invitation letter to health professionals centrally. The core programme went through formal approval procedure and was certified centrally. Novo Nordisk's regional sales managers and sales representatives were instructed that they could modify the meetings locally as long as the medical content was sufficient. Consultations took place between the local representatives and Novo Nordisk's medical department for such modifications before they were agreed. Finally, invitations were sent out by the local representatives to health professionals.

Novo Nordisk stated that information sessions were held as Levemir was a new medicine and the company had a responsibility to provide health professionals with accurate medical information on its use.

Information session at a restaurant on 18 June 2004

Novo Nordisk stated that this meeting was held on a floating restaurant. The entire restaurant had to be hired in order to avoid information on Levemir being inadvertently disseminated to the general public, as otherwise privacy could not be assured. The meeting was attended by ninety-five health professionals, mainly senior hospital doctors (consultant diabetologists) and diabetes specialist nurses who had responsibilities caring for people with diabetes, from the South East. They were invited by Novo Nordisk diabetes care specialists (sales representatives) in their local regions. Guests arrived at 7pm and were welcomed with a glass of champagne and canapés. At 7.35 pm the presentations began. The meeting was chaired by a consultant diabetologist. The speakers were a principal investigator of a large clinical trial on Levemir, a Swiss consultant diabetologist, who had first-hand experience with Levemir as Levemir was launched in Switzerland in March 2004, and the medical manager, Novo Nordisk. The presentations were of a high scientific quality; Novo Nordisk offered to supply copies of the slides. At 9pm the consultant diabetologist chaired a discussion and the formal proceedings ended at 9.15pm. Following this a standing buffet was served, with drinks and musical entertainment. The total cost of the event was £9,125.25. This was equivalent to £96.06 a head.

Novo Nordisk noted that a central location was necessary for the ease of travel for health professionals from all over the South East. Exclusive use of any venue, with drinks and dinner would incur certain costs (in this case the hire of the restaurant itself cost £2,800). Dinner had to be provided as many of the health professionals had spent a significant amount of travel time after work to get to the venue and it would be unreasonable not to provide a decent evening meal at 9.15pm. Novo Nordisk did not consider that the per head cost of £96.06, which included exclusive use of the venue to exclude general public, audiovisual equipment, drinks, dinner and entertainment, was excessive.

The medical content was informative; the principal trial investigator explained the clinical trial data; an international speaker, the consultant diabetologist shared his experience on Levemir and Novo Nordisk's medical manager presented pre-clinical data and data overview on Levemir. The three presentations with discussion took place between 7.35pm to 9.15pm. Novo Nordisk considered this to be a reasonable time for an educational session in the evening.

In summary, the level of hospitality at a central venue was not excessive given the medical content, including an international speaker and a UK speaker of professorial level.

In response to a request for further information, Novo Nordisk stated that the actual cost of the meeting was £11,020.63. Although the meeting was planned for 145 people, only 95 customers attended.

Information session at a football club venue, 21 June 2004

Novo Nordisk stated that this meeting was held in a private function room at a football club venue. Twenty-two health professionals, with responsibilities for caring for people with diabetes, from two centres attended. These included consultant diabetologists, diabetes specialist nurses, specialist registrars and senior house officers in diabetes. They were invited by their local Novo Nordisk diabetes care specialist.

The local Novo Nordisk diabetes care specialist gave a presentation on Levemir followed by another presentation on clinical data by the Levemir product manager. This was followed by a question and answer session. The presentations took place between 6pm and 7pm, and discussion continued as buffet and drinks arrived at 7pm. Discussion ended at 7.30pm.

The venue was organised through a recommendation by a consultant physician who was also the physician of the football club. Novo Nordisk noted that there was no personal gain for the doctor concerned. Costs were £150 for room hire, as well as £17.50 per person for a finger buffet. Wine was also provided. Drinks were available from the bar after the meal, but very little was served. In addition, a plasma screen was hired for £145.

The overall cost of £1,236.20 (excluding VAT) was therefore not excessive when set in the context of 90 minutes of medical presentation and discussion.

At 7.45pm, the plasma screen was used to show the live broadcast of the Euro 2004 England v Croatia football match. As this was shown for free on national television, Novo Nordisk did not consider this was inappropriate hospitality as, for example,

attending a live football or rugby game would have been. In fact, only 12-15 attendees stayed to watch the football.

Novo Nordisk noted that Clause 19.1 of the Code stated that 'the hospitality provided for a scientific meeting must not be… out of proportion to the occasion'. In Novo Nordisk's view, the hospitality for both the events were not out of proportion, and were not beyond the level of what the audience would adopt themselves.

PANEL RULING

The Panel noted that Clause 19.1 of the Code permitted companies to provide hospitality to members of health professions and appropriate administrative staff in association with scientific meetings, promotional meetings, scientific congresses and other such meetings. Hospitality must be secondary to the purpose of the meeting. The level of hospitality offered must be appropriate and not out of proportion to the occasion. The costs involved must not exceed the level which the recipients would normally adopt when paying for themselves.

The supplementary information stated, *inter alia*, that meetings organised for groups of doctors, other health professionals and/or for administrative staff which were wholly or mainly of a social or sporting nature were unacceptable. In determining whether a meeting was acceptable, consideration must be given to the educational programme, overall cost, facilities offered by the venue, nature of the audience, hospitality provided and the like. It should be the programme that attracted delegates and not the associated hospitality or venue.

The Panel considered each meeting separately. The invitation to the meeting in the restaurant (ref DM/054/0404) stated that guests would be welcomed from 7pm onwards by a reception drink, followed by a presentation summarising the major Levemir clinical studies. A barbecue would be available from 8.45pm onwards. There was no mention on the invitation as to who the speakers would be; it appeared that there would be only one presentation. The letter referred to 'the panel' being available during the evening to answer any questions about Levemir. The identity of the panel was not given but readers might have assumed that it consisted of the three people whose names appeared at the bottom of the letter; Novo Nordisk's medical manager and two sales managers.

In the Panel's view invitees would assume, given the wording of the invitation, that the educational part of the evening would last from approximately 7.30pm-8.45pm. The Panel noted Novo Nordisk's submission that the presentations had in fact lasted from 7.35pm to 9.15pm ie an hour and forty minutes.

The Panel noted that the final bill for the evening was £11,020.63 for 95 attendees. The cost per head was thus £116 which included payment for four musicians (£1,000) and two samba dancers (£700). The Panel noted that the evening had started with champagne and canapés.

The Panel considered that the arrangements for the meeting were unacceptable. The hospitality provided was out of proportion to the occasion and in the Panel's view the cost was more than the recipients would normally adopt when paying for themselves. Delegates would be attracted to the meeting because of the venue and the hospitality, not because of the programme. The impression created by the arrangements was important. A breach of Clause 19.1 was ruled.

With regard to the second meeting at issue, the Panel noted that the letter of invitation (ref DM/054/0404) highlighted the following in red type: 'The Executive Suite of [a local football club] Venue [local area]; 5.30pm; midsummer buffet dinner & drinks … 7.00pm … 7.45pm … Euro 2004 with the England v Croatia football game; Please confirm your attendance'. The Panel considered that the invitation was such that it sought to attract attendees to the meeting by virtue of the venue and the associated hospitality and not the educational content.

The Panel noted that the invitation to the meeting stated that delegates would be welcomed from 5.30pm onwards with a drink and canapés. There would then be a presentation on Levemir before a buffet dinner was served at 7pm followed by the football match, viewed on a plasma screen, at 7.45pm. The bar was to remain open during the match. In the Panel's view invitees would assume that the education part of the meeting would last no more than an hour.

The Panel noted that the total cost of the meeting was £1,452.53 (including VAT). The invoice indicated that there were 32 delegates; the cost per head was thus £45.39. The Panel noted that the meeting had started with champagne and canapés.

The Panel considered that the arrangements for the meeting were unacceptable. The hospitality provided was out of proportion to the occasion. In the Panel's view the evening was primarily a social and sporting event. The meeting appeared to have been arranged around a scheduled England football game. The impression created by the arrangements was important. A breach of Clause 19.1 was ruled.

Overall the Panel was extremely concerned about the arrangements for the meetings. Although Novo Nordisk had submitted that core programmes had been agreed centrally, local representatives had been able to adapt these for their own needs but such modifications had been agreed with Novo Nordisk's medical department. The two letters of invitation bore reference numbers suggesting that they had been approved under the Code. The Panel noted that it could not make any ruling under Clause 2 of the Code as no allegation of a breach of that clause had been alleged. Given the circumstances the Panel considered that had such an allegation been made it would have ruled a breach of Clause 2 as a sign of particular censure. The Panel decided to report Novo Nordisk to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

During the consideration of this case the Panel noted that both invitations invited the recipients to an information session. The bottom right hand corner of each letter stated 'This educational meeting is

sponsored by Novo Nordisk'. The Panel was concerned that some delegates might have assumed that the meetings were non-promotional which was not so. Each delegate had been provided with copies of three relevant scientific posters as well as a Levemir leavepiece. The Panel was also concerned that, given the nature of the meetings, the letters of invitation had not included the Levemir prescribing information. The Panel requested that Novo Nordisk be advised of its concerns.

COMMENTS FROM NOVO NORDISK

Novo Nordisk provided the requisite undertaking and assurance and stated that the company took this matter seriously and had since tightened up its procedures. Letter templates written by the medical department would be available only in secure format and the sales team would be strictly barred from altering the content. Although certification of meetings held in the UK was not required under the Code, Novo Nordisk now required its sales team to send meeting invitations to the medical department for approval in order to ensure that the letters were written to a high standard.

At the consideration of the report the Novo Nordisk representatives provided details of changes to the advice for company sponsored meetings. The representatives stated that the planning for the UK launch meetings had started at the end of February 2004. Novo Nordisk's view was that the event in London was not excessive in terms of cost or the image it created. The meeting at the local football club venue was arranged prior to the date of the football match being known. The cost was not excessive and the venue was low key.

APPEAL BOARD CONSIDERATION

The Appeal Board was extremely concerned about the arrangements for the two meetings; the impression created was unacceptable. Delegates would not be primarily attracted by the programme but by the associated hospitality. The Appeal Board also noted fundamental errors in the content of the letter template provided to the representatives. There appeared to be a lack of understanding of the requirements of the Code at head office level. The Appeal Board decided that, as set out in Paragraph 10.4 of the Constitution and Procedure, Novo Nordisk should be required to undergo an audit of its procedures relating to the Code. This would be carried out as soon as possible. Following receipt of the audit report, the Appeal Board would then consider whether further action was necessary.

FURTHER CONSIDERATION BY THE APPEAL BOARD

Upon receipt of the audit report the Appeal Board decided that the company should be re-audited within the next month. Upon receipt of the report of the follow-up audit the Appeal Board would decide whether further action was necessary.

Upon receipt of the report on the follow-up audit, the Appeal Board noted that progress had been made. It was concerned that there was no representatives' briefing material for Kliovance, Levemir or Novo Seven. Novo Nordisk stated that this would be available by its May sales conference. The Appeal Board also noted from the audit report that representatives must be given written instructions on the application of the Code.

The Appeal Board adjourned its consideration of the audit report in order for Novo Nordisk to provide the Authority with copies of the representatives' briefing material and assurances with regard to representatives' instructions on the application of the Code. Following assessment by the Authority of these items the Appeal Board decided that Novo Nordisk should resubmit the representatives' briefing material for Novo Seven as it was inadequate. Following the Authority's assessment of the revised Novo Seven representatives' briefing material the Appeal board decided that no further action was required.

Complaint received	**6 July 2004**
Undertaking received	**13 August 2004**
PMCPA proceedings completed	**15 September 2005**

CASE AUTH/1697/3/05

GLAXOSMITHKLINE v TAKEDA

Promotion of Actos

GlaxoSmithKline complained about an Actos (pioglitazone) journal advertisement and primary care mailing issued by Takeda. Both presented detailed results of a head-to-head clinical trial (Goldberg *et al* 2004) comparing the effects of pioglitazone and rosiglitazone (GlaxoSmithKline's product Avandia) on lipid parameters. Actos and Avandia were oral hypoglycaemic agents for use in type 2 diabetes.

GlaxoSmithKline stated that in both pieces, mention of the glucose-lowering effects of pioglitazone and rosiglitazone (their sole indication) was restricted to one sentence. The remainder of both the journal advertisement and the mailing was devoted to lipid effects, including a table of lipid-related results that alone took up approximately half of the total space devoted to copy. Neither pioglitazone nor rosiglitazone was indicated for the improvement of lipid profiles.

GlaxoSmithKline noted that in Case AUTH/1580/4/04 an advertisement was ruled in breach of the Code because, in the Panel's view, the effects of rosiglitazone on blood pressure had been unduly emphasised over its antihyperglycaemic effects. GlaxoSmithKline alleged that, in this light, the imbalance in the pioglitazone materials was clearly in breach of the Code.

The Panel noted that, although very similar, the copy and layout of the journal advertisement and the mailing were different and so it decided to make separate rulings.

The journal advertisement was headed 'news….news…..news….' followed by 'Head-to-head study in Type 2 diabetes: pioglitazone outperforms rosiglitazone on lipid parameters whilst demonstrating equivalent glycaemic control'. The second half of the sentence was written in red. There then followed a summary of the results of Goldberg *et al*. Prominent within the advertisement was a table of data comparing the percentage change in lipid parameters from baseline at week 24 in patients treated with either pioglitazone or rosiglitazone. Each parameter was statistically significant for Actos.

The Panel noted that Actos was an oral hypoglycaemic agent for use alone or in combination in sub-populations of type 2 diabetics. The Panel considered, however, that the primary theme of the advertisement was the possible beneficial effect that pioglitazone had on lipid parameters. The reader's eye would be drawn to the claim 'pioglitazone outperforms rosiglitazone on lipid parameters whilst demonstrating equivalent glycaemic control', in red, and the table of data. The Panel considered that the advertisement implied that Actos was licensed for the management of lipid profiles in type 2 diabetics which was not so. This was inconsistent with the marketing authorization and misleading in that regard. Breaches of the Code were ruled.

With regard to the mailing, the Panel noted that the envelope referred to a head-to-head pioglitazone vs rosiglitazone study. The leaflet inside was folded and printed such that recipients would expect 'head-to-head line news'. Once unfolded the leaflet was headed, in red, 'Summary of head-to-head study results presented at the American Heart Association annual meeting – potentially important implications for the management of Type 2 diabetes'. There then followed a discussion of Goldberg *et al* in the light of current guidance from the National Institute for Clinical Excellence (NICE) which suggested that the effectiveness of glitazone therapy should not only be monitored in terms of glycaemic control, but also by impact on other cardiovascular risk factors such as lipid profile. The leaflet featured the same table of results from Goldberg *et al* as appeared in the advertisement. The table was sub-headed 'head-to-head lipid comparison: pioglitazone outperforms rosiglitazone'.

The Panel considered that the primary theme of the leaflet was the effect of pioglitazone on lipid parameters compared with rosiglitazone. The reader's eye would be drawn to the table of results and the sub-heading 'lipid comparison: pioglitazone outperforms rosiglitazone'. Although the effects of the two products on glycaemic control (HbA_{1c}) was discussed, this was within a less prominent body of text above the table and thus was easily overlooked. The Panel considered that the leaflet implied that Actos was licensed for the management of lipid profiles in type 2 diabetics which was not so. This was inconsistent with the marketing authorization and misleading in that regard. Breaches of the Code were ruled.

Upon appeal by Takeda, the Appeal Board noted that the management of plasma lipid profiles was an important aspect of the treatment of type 2 diabetes. Doctors would want to know that, at the very least, a medicine which they gave to lower blood sugar did not, at the same time, have an adverse effect on plasma lipids. In this respect the Appeal Board noted the parties' submission at the appeal that, as part of a marketing authorization application for the glitazones, companies were obliged to collect data on their effects on plasma lipids. The Appeal Board further noted the statement in the pioglitazone summary of product characteristics (SPC) regarding its effects on plasma lipids together with the statement 'An outcome study is underway with pioglitazone, and until this is completed the long-term benefits associated with improved metabolic control have not been demonstrated'. Nonetheless the Appeal Board considered that the different effects of pioglitazone and rosiglitazone on plasma lipids was an aspect of therapy that would be important to prescribers.

With regard to the advertisement, the Appeal Board noted the statement 'Whether these differences translate into differences for the future risk of CVD has yet to be determined' beneath the table of data. Data on the lipid effects of pioglitazone had been submitted as part of the marketing authorization application and Section 5.1 of the SPC detailed those

effects. The Appeal Board did not consider that the advertisement suggested that Actos was licensed for the management of lipid profiles in type 2 diabetics and in that regard it was neither inconsistent with the marketing authorization nor misleading as alleged. The Appeal Board ruled no breach of the Code.

With regard to the mailing, the Appeal Board noted that the leaflet was headed, in red, 'Summary of head-to-head study results presented at the American Heart Association annual meeting – potentially important implications for the management of Type 2 diabetes'. The indication thus appeared in the heading. There then followed a discussion of Goldberg *et al* in the light of current guidance from NICE which suggested that the effectiveness of glitazone therapy should not only be monitored in terms of glycaemic control, but also by impact on other cardiovascular risk factors such as lipid profile. The leaflet featured the same table of results from Goldberg *et al* as appeared in the advertisement. Although there was a statement to the effect that the impact of the differences noted in the table on long-term outcomes had yet to be determined, the Appeal Board noted that the heading clearly stated '*potentially* important implications …' (emphasis added). The Appeal Board noted its general comments above regarding the importance of lipid profiles in the treatment of type 2 diabetes. The Appeal Board did not consider that the mailing implied that Actos was licensed for the management of lipid profiles in type 2 diabetics and in that regard it was neither inconsistent with the marketing authorization nor misleading. No breach of the Code was ruled.

GlaxoSmithKline noted that the journal advertisement stated that the comparison was carried out in 'over 800' patients with type 2 diabetes which did not correspond with its understanding of the data; Takeda had confirmed that, while 802 patients were randomised into the study, a maximum of 735 were involved in the head-to-head lipid comparison. While this discrepancy might not be clinically significant, 'over 800' was inaccurate and therefore in breach of the Code.

The Panel noted that, following recruitment into the trial, 802 patients entered a placebo washout phase for 4 weeks followed by 24 weeks of either pioglitazone or rosiglitazone monotherapy. The published abstract from Goldberg *et al* gave a table of results showing changes from baseline at 24 weeks for those patients treated with pioglitazone (n=363) and rosiglitazone (n=356). This table of results formed the basis of the table of data given in the advertisement and the mailing. Both the advertisement and mailing implied that the results shown related to more than 800 patients which was not so. The materials were inaccurate and misleading in that regard. A breach of the Code was ruled which was upheld upon appeal by Takeda.

GlaxoSmithKline UK Limited complained about an Actos (pioglitazone) journal advertisement (ref AC 041208c) and a primary care mailing (ref AC041207a) issued by Takeda UK Ltd. Both pieces presented detailed results of a head-to-head clinical trial (Goldberg *et al* 2004) comparing the effects of pioglitazone and rosiglitazone (GlaxoSmithKline's product Avandia) on lipid parameters. Actos and Avandia were oral hypolglycaemic agents for use in type 2 diabetes.

Intercompany correspondence had failed to resolve the issue.

1 The effects of pioglitazone on plasma lipid profile

COMPLAINT

GlaxoSmithKline stated that in both pieces mention of the glucose-lowering effects of pioglitazone and rosiglitazone (their sole indication) was restricted to one sentence. The remainder of both the journal advertisement and the mailing was devoted to lipid effects, including a table of lipid-related results that alone took up approximately half of the total space devoted to copy. Neither pioglitazone nor rosiglitazone was indicated for the improvement of lipid profiles.

GlaxoSmithKline noted that in a previous case (Case AUTH/1580/4/04) it was ruled in breach of Clause 7.2 of the Code for an advertisement in which, in the judgement of the Panel, the effects of rosiglitazone on blood pressure had been unduly emphasised over its antihyperglycaemic effects. GlaxoSmithKline alleged that, in this light, the imbalance in the pioglitazone materials was clearly in breach of Clauses 3.2 and 7.2 of the Code.

RESPONSE

Takeda noted that the materials in question referred to new clinical trial data which were presented at the American Heart Association meeting last November, and were described as such in both items with the phrase 'Summary of the results' being a key heading that was used. Within the confines of a single page, the design aspects of the study were referred to as being a 'Double blind comparison of pioglitazone and rosiglitazone in over 800 patients with Type 2 diabetes and dyslipidaemia'.

Takeda submitted that GlaxoSmithKline was incorrect to state that 'mention of the glucose-lowering effects of the two products was restricted to one sentence'. The main heading in the journal advertisement stated 'pioglitazone outperforms rosiglitazone on lipid parameters whilst demonstrating equivalent glycaemic control' and was again repeated in the text above the table which stated that 'the treatments provided similar glycaemic control'. In the mailing, once again, 'similar glycaemic control' was the first result mentioned. Thus Takeda submitted that sufficient attention had been given to mentioning glycaemic control in a study which was designed to test the hypothesis that pioglitazone was superior to rosiglitazone with respect to lipid-lowering potential, and where glycaemic control was one of several secondary end points.

Takeda noted that, in addition, GlaxoSmithKline had alleged that in mentioning these effects on lipids Takeda had referred to an unlicensed indication.

Takeda submitted that this was incorrect, patients in the study all had type 2 diabetes and received either pioglitazone or rosiglitazone to control their blood glucose levels, where the efficacy for both products was well established and might be considered as similar. The study was powered to detect any difference in the secondary treatment effects of long-term, satisfactory glycaemic control with glitazones, namely lipids. Thus the results of the study in the materials at issue were clearly presented in the context of treating patients for their type 2 diabetes (glycaemic control). Furthermore, the effects of pioglitazone on lipid parameters (again within the context of the primary indication of glycaemic control) was acknowledged in the Actos summary of product characteristics (SPC) where Section 5.1 stated 'In most clinical trials reduced total plasma triglycerides and free fatty acids and increased HDL-cholesterol levels were observed compared to placebo, with no statistically significant increases in LDL-cholesterol'.

Takeda noted GlaxoSmithKline's allegation that the table of lipid-related results 'took up approximately half the total space devoted to copy'. Takeda submitted that this was incorrect for both items. Considering printed copy and paper dimensions, for the journal advertisement the table took up 18% of the page and for the mailer it was 14%.

Takeda noted GlaxoSmithKline's comparison with respect to Case AUTH/1590/5/04, where factually incorrect claims were made concerning rosiglitazone being able to 'help you meet your blood pressure GMS targets' and that 'using the right oral antidiabetic agent can also help lower blood pressure'. Takeda submitted that in contrast to the GlaxoSmithKline advertisement, the material now at issue simply displayed the results and did not make any claims concerning the data nor indeed any claims which were outside the licence. The caveat was even given that 'Whether these differences translate into differences for future risk of CVD [cardiovascular disease] has yet to be determined' so as to prevent any erroneous claims or conclusions being drawn. No such caveats were given in the Avandia/Avandamet advertisements, whereas the beneficial effects of pioglitazone were mentioned in Section 5.1 of the Actos SPC, no such beneficial effects on blood pressure were contained within the Avandia and Avandamet SPCs.

Takeda denied breaches of Clauses 3.2 and 7.2 of the Code.

PANEL RULING

The Panel noted that, although very similar, the copy and layout of the journal advertisement and the mailing were different and so it decided to make separate rulings.

The journal advertisement was headed 'news….news…..news….' followed by 'Head-to-head study in Type 2 diabetes: pioglitazone outperforms rosiglitazone on lipid parameters whilst demonstrating equivalent glycaemic control'. The second half of the sentence was written in red. There then followed a summary of the results of Goldberg *et al*. Prominent within the advertisement was a table of data comparing the percentage change in lipid parameters from baseline at week 24 in patients treated with either pioglitazone or rosiglitazone. Each parameter was statistically significant for Actos.

The Panel noted that Actos was an oral hypoglycaemic agent indicated as either oral monotherapy or in combination in sub-populations of type 2 diabetics. The Panel considered, however, that the primary theme of the advertisement was the possible beneficial effect that pioglitazone had on lipid parameters. The reader's eye would be drawn to the claim 'pioglitazone outperforms rosiglitazone on lipid parameters whilst demonstrating equivalent glycaemic control', in red, and the table of data. The Panel considered that the advertisement implied that Actos was licensed for the management of lipid profiles in type 2 diabetics which was not so. This was inconsistent with the marketing authorization and misleading in that regard. Breaches of Clauses 3.2 and 7.2 respectively were ruled.

With regard to the mailing, the Panel noted that the envelope referred to a head-to-head pioglitazone vs rosiglitazone study. The leaflet inside was folded and printed such that recipients would expect 'head-to-head line news'. Once unfolded the leaflet was headed, in red, 'Summary of head-to-head study results presented at the American Heart Association annual meeting – potentially important implications for the management of Type 2 diabetes'. There then followed a discussion of Goldberg *et al* in the light of current guidance from the National Institute for Clinical Excellence which suggested that the effectiveness of glitazone therapy should not only be monitored in terms of glycaemic control, but also by impact on other cardiovascular risk factors such as lipid profile. The leaflet featured the same table of results from Goldberg *et al* as appeared in the advertisement. The table was sub-headed 'head-to-head lipid comparison: pioglitazone outperforms rosiglitazone'.

The Panel considered that the primary theme of the leaflet was the effect of pioglitazone on lipid parameters compared with rosiglitazone. The reader's eye would be drawn to the table of results and the sub-heading 'lipid comparison: pioglitazone outperforms rosiglitazone'. Although the effects of the two products on glycaemic control (HbA_{1c}) was discussed, this was within a less prominent body of text above the table and thus was easily overlooked. The Panel considered that the leaflet implied that Actos was licensed for the management of lipid profiles in type 2 diabetics which was not so. This was inconsistent with the marketing authorization and misleading in that regard. Breaches of Clauses 3.2 and 7.2 respectively were ruled.

APPEAL BY TAKEDA

Takeda noted that the advertisement clearly stated that it related to a 'Head-to-head study in Type 2 diabetes' and was a 'Summary of results presented at the November 2004 meeting of the American Heart Association in New Orleans'. The text gave some details of the study design.

Takeda submitted that neither the advertisement nor the mailing contained any information which suggested a new indication for pioglitazone, nor indeed what that new indication might be. Furthermore with regard to lipid profiles both pieces stated 'Whether these differences translate into differences for the future risk for CVD has yet to be determined'. This statement implied that the overall clinical benefit of these lipid changes had yet to be proven for pioglitazone.

Takeda noted that dyslipidaemia was a well recognised risk factor for cardiovascular disease in type 2 diabetics. Large scale intervention studies (eg UKPDS) had highlighted the impact of dyslipidaemia in diabetes. Outcome studies with statins and fibrates (eg 4S, CARDS, VA-HIT) had demonstrated the benefit of improving lipid profiles in diabetics.

Finally in accordance with Clause 4 of the Code, the prescribing information was provided with both the advertisement and the mailing which had clearly given the indication and provided information concerning pioglitazone's effects on lipid parameters: 'In most clinical trials, reduced total plasma triglycerides and free fatty acids, and increased HDL-cholesterol levels were seen, with no statistically significant increases in LDL-cholesterol levels.'

Takeda noted that the Panel had not acknowledged that Section 5.1 of the Actos SPC contained a large section of information concerning pioglitazone's effects on plasma triglycerides, free fatty acids, HDL-cholesterol and LDL-cholesterol as follows:

'In most clinical trials, reduced total plasma triglycerides and free fatty acids, and increased HDL-cholesterol levels were observed as compared to placebo, with no statistically significant increases in LDL-cholesterol levels. In clinical trials of up to two years' duration pioglitazone reduced total plasma triglycerides and free fatty acids, and increased HDL-cholesterol levels, compared with placebo, metformin or gliclazide. Pioglitazone did not cause statistically significant increases in LDL-cholesterol level compared with placebo, whilst reductions were observed with metformin and gliclazide. In a 20 week study, as well as reducing fasting triglycerides, pioglitazone reduced postprandial hypertriglyceridaemia through an effect on both absorbed and hepatically synthesised triglycerides. These effects were independent of pioglitazone's effects on glycaemia and were statistically significant different to glibenclamide.'

Takeda submitted that the journal advertisement and mailing had simply served to give further corroborating evidence from a new double-blind study in this area and had not made any further claims other than highlighting that the effects of pioglitazone on lipids were found to be significantly different than those for rosiglitazone. The results were simply presented in a tabulated form with p values given; a well established format for presenting study results. In addition, there was the caveat that 'Whether these differences translate into differences for the future risk for CVD has yet to be determined'. Takeda did not consider that the material implied 'clinical significance'.

Finally, Takeda refuted any similarities between the present case and Case AUTH/1580/4/04 where claims regarding the antihypertensive effects of rosiglitazone were made and how these could 'help you achieve your blood pressure General Medical Services (GMS) targets'. This appeared to be a claim outside of licence and a claim to achieving GMS targets. There was no mention of any beneficial effects on blood pressure in the Avandia or Avandamet SPCs. In contrast, the advertisement and mailing at issue in the present case (Case AUTH/1697/3/05) simply displayed the results of the study without making any claims.

COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline alleged that in the promotional items at issue, the lipid effects were unduly emphasised and would lead the average reader to assume that pioglitazone was indicated for the management of lipid profiles. This selective use of the data had exaggerated the benefit of pioglitazone. Neither pioglitazone nor rosiglitazone were indicated for lipid improvements.

GlaxoSmithKline alleged that while lipid improvements were mentioned in Section 5.1 of the pioglitazone SPC, these were pharmacodynamic effects of the medicine, and not primary proof of efficacy, unrelated to the primary indication. As such these effects had been presented in an unbalanced way without the context of the primary indication. GlaxoSmithKline noted that it had been ruled in breach of Clause 7.2 for giving undue emphasis to the effects of Avandamet on blood pressure (Case AUTH/1590/5/04). The Medicines and Healthcare products Regulatory Agency had also stated that, while it was permissible to refer to non-glycaemic effects in promotional materials, the emphasis on such effects should be secondary to the licensed indication, and should not be given equal prominence.

GlaxoSmithKline noted that the results presented in the table were statistically significant although by Takeda's own admission, the clinical relevance of these findings remained in doubt, particularly when considered in the context of targets as set by the International Diabetes Federation and the European Diabetes Policy Group.

GlaxoSmithKline alleged that large scale clinical trials (eg CARDS) formed the evidence base for recommending the use of statins in patients with type 2 diabetes. These studies had established the beneficial effect of statins in this patient group. Glitazones by targeting insulin resistance had a wide array of effects on a large number of cardiovascular risk factors (Greenberg 2003). It was certainly possible that these other factors were more important in reducing cardiovascular disease. In addition, when pioglitazone and rosiglitazone were administered with background statin therapy, no significant differences in mean percentage change in LDL-C had been observed (Lewin *et al* 2004).

In summary, GlaxoSmithKline concurred with the Panel's view that the materials in question were inconsistent with the marketing authorization and therefore misleading.

APPEAL BOARD RULING

The Appeal Board noted that the management of plasma lipid profiles was an important aspect of the treatment of type 2 diabetes. Doctors would want to know that, at the very least, a medicine which they gave to lower blood sugar did not, at the same time, have an adverse effect on plasma lipids. In this respect the Appeal Board noted the parties' submission at the appeal that as part of a marketing authorization application for the glitazones companies were obliged to collect data on their effects on plasma lipids. The Appeal Board further noted the statement in the pioglitazone SPC regarding its effects on plasma lipids together with the statement 'An outcome study is underway with pioglitazone, and until this is completed the long-term benefits associated with improved metabolic control have not been demonstrated'. Nonetheless the Appeal Board considered that the different effects of pioglitazone and rosiglitazone on plasma lipids was an aspect of therapy that would be important to prescribers.

With regard to the advertisement the Appeal Board noted that the statement 'Whether these differences translate into differences for the future risk of CVD has yet to be determined' appeared beneath the table of data. Data on the effect of pioglitazone on lipids had had to be submitted as part of the marketing authorization application and Section 5.1 of the SPC contained details of those effects. The Appeal Board did not consider that the advertisement suggested that Actos was licensed for the management of lipid profiles in type 2 diabetics and in that regard it was neither inconsistent with the marketing authorization nor misleading as alleged. The Appeal Board ruled no breach of Clauses 3.2 and 7.2 of the Code. The appeal on this point was successful.

With regard to the mailing, the Appeal Board noted that the leaflet was headed, in red, 'Summary of head-to-head study results presented at the American Heart Association annual meeting – potentially important implications for the management of Type 2 diabetes'. The indication thus appeared in the heading. There then followed a discussion of Goldberg *et al* in the light of current guidance from the National Institute for Clinical Excellence which suggested that the effectiveness of glitazone therapy should not only be monitored in terms of glycaemic control, but also by impact on other cardiovascular risk factors such as lipid profile. The leaflet featured the same table of results from Goldberg *et al* as appeared in the advertisement. Although there was a statement to the effect that the impact of the differences noted in the table on long-term outcomes had yet to be determined the Appeal Board noted that the heading clearly stated '**potentially** important implications …' (emphasis added). The Appeal Board noted its general comments above regarding the importance of lipid profiles in the treatment of type 2 diabetes. The Appeal Board did not consider that the mailing implied that Actos was licensed for the management of lipid profiles in type 2 diabetics and in that regard it was neither inconsistent with the marketing authorization nor misleading. No breach of Clauses 3.2 and 7.2 was ruled. The appeal on this point was thus successful.

2 Patient numbers

COMPLAINT

GlaxoSmithKline noted that the journal advertisement stated that the comparison was carried out in 'over 800' patients with type 2 diabetes. GlaxoSmithKline alleged that this figure did not correspond with its understanding of the data; Takeda had confirmed that, while 802 patients were randomised into the study, a maximum of 735 was actually involved in the head-to-head lipid comparison. While this discrepancy might not be clinically significant, the figure cited in the advertisement was, by Takeda's own admission, inaccurate and therefore in breach of Clause 7.2 of the Code.

RESPONSE

Takeda noted that GlaxoSmithKline had alleged that the study included over 800 patients yet 'the number of patients reported as having undergone lipid investigations was considerably lower'. The phrase 'considerably lower' was refuted. Takeda submitted that of the 802 patients who were randomised, 735 (91%) received study medication and therefore fulfilled the criteria for the Full Analysis Set. This figure was well in excess of the 600 patients required to complete the study so as to fulfil the requirements of the prospectively determined statistical plan, designed to give sufficient power to test the primary hypothesis. Consequently as the main analysis was conducted on a higher number of patients than originally planned, the power of the study had been increased which served to further confirm the study conclusions that pioglitazone outperformed rosiglitazone on lipid parameters whilst demonstrating equivalent glycaemic control.

Takeda denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that although 802 patients were recruited into the trial they entered a placebo washout phase for 4 weeks followed by 24 weeks of either pioglitazone or rosiglitazone monotherapy. The published abstract from Goldberg *et al* gave a table of results showing changes from baseline at 24 weeks for those patients treated with pioglitazone (n=363) and rosiglitazone (n=356). This table of results formed the basis of the table of data given in the advertisement and the mailing. Both the advertisement and mailing implied that the results shown related to more than 800 patients which was not so. The materials were inaccurate and misleading in that regard. A breach of Clause 7.2 was ruled.

APPEAL BY TAKEDA

Takeda submitted that the size and scope of the study was given in the text above the table, namely that over 800 patients (802 to be precise) were randomised into the study. That 69 patients withdrew during the placebo washout phase was irrelevant as it had not affected the statistical power of the study nor the validity of the results as the statistical section of the protocol prospectively defined the number of patients

required to complete either arm was 300. That 369 patients were treated with pioglitazone and 366 with rosiglitazone simply served to strengthen the conclusions which could be drawn from the study. Furthermore, all laboratory end points (apart from LDL particle size where p= 0.005) reached statistical significance (p<0.001), even though the statistical analysis only planned for a 5% level of significance.

Takeda submitted that the conclusions drawn from the study were accurate, balanced, fair, objective and not unambiguous. Moreover, the 69 withdrawals from the study were inconsequential to its outcome.

Takeda did not consider that including the number of patients entered into the study was inaccurate or that the results had been presented in an unfair and unbalanced way.

COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline noted that the patient number cited in the advertisement and mailing was inaccurate.

APPEAL BOARD RULING

The Appeal Board noted that although Goldberg *et al* reported that 802 patients were randomised into the study, results were shown for only 719 ie pioglitazone (n=363) and rosiglitazone (n=356). The Appeal Board thus considered that it would have been correct to state that 'over 800' patients had been recruited, but not to imply that the results shown related to all of those patients. The advertisement and mailing were misleading in that regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

Complaint received **23 March 2005**

Case completed **5 September 2005**

CASE AUTH/1703/4/05 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER v TAKEDA

Market research questionnaire

A general practitioner complained about a market research questionnaire, noting that the covering letter suggested that the exercise was legitimate 'research' with its findings being of a degree of importance to the reader. The questionnaire, however, appeared rather than to inquire about general influences on prescribing, to ask for the names of specific local colleagues and thus was merely an attempt to generate a list of names of local opinion leaders so they could be targeted by a pharmaceutical company. The complainant noted that the questionnaire focussed on cardiology and was told by the market research agency that Takeda had commissioned it and that the company was launching a 'new cardio protective' medicine.

The complainant considered that the letter and the 'research' were bogus. It was an attempt to gain sensitive information under a false pretence. He alleged a breach of the Code and noted the inappropriate financial inducement.

The Panel noted Takeda's submission that the material was market research. The Code required that such activity must not be disguised promotion. The Panel did not consider that it was unacceptable for Takeda to have commissioned market research to validate its understanding of the networks that existed between secondary and primary care in cardiology.

The Panel was concerned about the material. The Panel noted Takeda's submission that it had not intended to use the information provided to make a database of target health professionals. The Panel also noted Takeda's submission that the responders had given their consent for their details and response to be provided to Takeda. The Panel queried whether this was so. A specimen covering letter sent with the questionnaire by the market research agency explained that the information submitted in the survey might be disclosed to healthcare companies, medical authorities, government bodies and other commercial organisations concerned with the promotion of distribution and development of products and services to the NHS. No such explanation appeared in the questionnaire itself. The Panel noted the material did not state that it was sponsored by a pharmaceutical company as required by the Code. The description of the various groups to whom the data would be disclosed would not suffice in this regard. There was however, no allegation on this point. The Panel did not consider that the responders had been given sufficient information such that they had given consent to the disclosure of their details and response. The Panel also queried whether the payment of £30 high street vouchers was excessive; the questionnaire was straightforward and a relevant database quoted £14.50 as a fee for completing a simplistic post-market surveillance form.

The Panel was concerned about the material; participants did not know that it was activity undertaken on behalf of a pharmaceutical company to whom their details and the information provided would be disclosed. Nonetheless the material was not such as to constitute disguised promotion of a specific medicine and the Panel was thus obliged to rule no breach of the Code.

A general practitioner complained about a market research questionnaire which asked recipients to supply the names, addresses and other details of

colleagues to whom they might turn for advice with regard to the management of hypertensive patients, and specifically those with heart failure. The covering letter stated that the results of the study were very important to understanding the role that informal communication played in addition to having a degree of importance to the recipient. Readers were offered an honorarium of £30 of high street vouchers in return for their participation.

* * * * *

It was initially unclear whether the market research survey in question was subject to the Code. Takeda UK Limited was twice asked for further information to clarify the position whereupon it was decided that the matter came within the scope of the Code.

* * * * *

COMPLAINT

The complainant noted that the covering letter suggested that the exercise was legitimate 'research' with its findings being of a degree of importance to the reader. The questionnaire, however, appeared rather than inquire about general influences on prescribing to ask for the names of specific local colleagues.

The complainant considered that rather than being useful 'research' this might merely be an attempt to generate a list of names of local opinion leaders so they could be targeted by a pharmaceutical company. The complainant noted that the questionnaire focussed on cardiology related questions. The complainant contacted the market research agency and was told that Takeda had commissioned the research and that the company was launching a 'new cardio protective' medicine.

The complainant considered that the letter and the 'research' were bogus. It was an attempt to gain sensitive information under a false pretence. The complainant alleged a breach of the Code and noted the inappropriate financial inducement.

When writing to Takeda the Authority asked it to respond in relation to Clause 10.2 of the Code.

RESPONSE

Takeda confirmed that it had commissioned the market research via a third party to validate the company's current understanding of the complex networks which existed between secondary and primary care across the UK in cardiology. The NHS was constantly changing and evolving and this was particularly true in cardiology as the NHS sought to meet the government's ambitious targets contained within the National Service Framework for Coronary Heart Disease. As for any other company involved in this area it was important for Takeda to keep track of these changes and to understand its customers and the influence the different parts of the NHS had on one another.

The agency conducting the research was a member of the British Healthcare Business Intelligence Association (BHBIA) and was a reputable organisation which aimed to provide a national coverage of a therapeutic area network with a focus on key healthcare units and NHS centres. The agency had also since confirmed that it understood that this piece of research was within of the remit of the guidance from the BHBIA.

Takeda submitted that it was not the purpose of this research to establish a database; the company already had access to lists of UK prescribers as this information was in the public domain. The results from this research had not yet been received from the agency and hence had not been analysed by Takeda. The data would help Takeda to look at whether secondary care influence was limited to a particular primary care trust or whether it extended beyond the boundary of a local health economy. The intent was to analyse the results alongside other appropriate available data regarding the NHS and its networks and to use this to plan the company's future strategy. There was no intention to use the personal data as Takeda already had access to the details of health professionals.

Takeda noted the complainant's concerns regarding the research and in particular that he had noted that the covering letter stated that the research findings would have a 'degree of importance to you'. It appeared that the complainant might have misinterpreted the letter which stated 'the results of this study are very important to understanding the role that informal communications plays as well as its degree of importance to you' ie the degree that informal communications were important to the individual doctor.

Takeda submitted that it had no intention to use the information collected to make a database of target health professionals; Takeda already had such lists. Further, the information given to the complainant by the agency was wrong in that although the company currently marketed products in the cardiovascular therapeutic area, it was not preparing to launch a cardio-protective medicine. Finally in relation to Clause 10.2, Takeda noted that this research was not product research and was not 'disguised promotion'.

Regarding the financial arrangements, Takeda considered that the honorarium payment of £30 high street vouchers was appropriate for the time spent by the respondent completing the questionnaire, based on the recommended scale of fees to be paid to doctors involved in clinical trials.

In response to a request for further information Takeda reiterated that the purpose of the survey was to validate the company's current understanding of the complex networks which existed between secondary and primary care across the UK in cardiology. It was not the purpose to compile a target list as Takeda UK already had lists of UK prescribers, their names, addresses, and therapeutic speciality.

Regarding the amount of information requested, the agency had confirmed that with this type of survey it was their normal practice to ask for a person's name, address and gender. The reason for this was to keep records of anyone that did not wish to be contacted by the agency for market research. If any of the

respondents or anyone they named as being in their network requested or had previously requested not to be a part of such research then the agency needed to take a note of this and not supply that information to Takeda. The agency collected the name, address and gender so that it could ensure that it could validate against its records who did not wish to take part in market research.

As the additional information regarding gender was not required by Takeda, the company would not request this information in future research of this nature.

Takeda stated that the marketing authorization for candesartan was changed in December 2004 with the addition of heart failure to the existing indication of hypertension. A mailing was sent to physicians to inform them of this new indication in January. The piece of market research in question was commissioned in February 2005.

In response to a further request for more information, Takeda stated that the market research questionnaire was mailed to a number of physicians. The details (names and addresses) of those physicians who responded to the questionnaire, and hence had their consent for the information to be used, were passed to Takeda along with the information that they provided about other physicians in their own network.

PANEL RULING

The Panel noted that the market research questionnaire had been sent out by a market research company on behalf of Takeda. It was an established principle under the Code that activities carried out with the authority of a pharmaceutical company were the responsibility of that pharmaceutical company even if a third party was involved. Takeda was thus responsible for the questionnaire.

The Panel noted Takeda's submission that the material was market research. Clause 10.2 of the Code required that such activity must not be disguised promotion. The Panel did not consider that it was unacceptable for Takeda to have commissioned market research to validate its understanding of the networks that existed between secondary and primary care in cardiology. The arrangements for such research must not contravene the Code. The Panel also noted that the supplementary information to Clause 10.2 of the Code drew attention to guidelines – The Legal and Ethical Framework for Healthcare Market Research – produced by the British Healthcare Business Intelligence Association in consultation with The Association of the British Pharmaceutical Industry. The framework document explained that database building was incompatible with market research; names and addresses of respondents should not be passed on to any third party and respondent details should not be placed onto a client database, used in the development of customer intelligence for the purposes of direct promotion and/or used for the purposes of direct marketing following research.

The Panel was concerned about the material. The Panel noted Takeda's submission that it had not intended to use the information provided to make a database of target health professionals. The Panel also noted Takeda's submission that the responders had given their consent for their details and response to be provided to Takeda. The Panel queried whether this was so. A specimen covering letter sent with the questionnaire by the market research agency explained that the information submitted in the survey might be disclosed to healthcare companies, medical authorities, government bodies and other commercial organisations concerned with the promotion of distribution and development of products and services to the NHS. No such explanation appeared in the questionnaire itself. The Panel noted the material did not state that it was sponsored by a pharmaceutical company as required by Clause 9.10 of the Code. The description of the various groups to whom the data would be disclosed would not suffice in this regard. There was however, no allegation on this point. The Panel did not consider that the responders had been given sufficient information such that they had given consent to the disclosure of their details and response. The Panel also queried whether the honorarium of £30 high street vouchers was excessive given the simplistic nature of the questionnaire. In this regard the Panel noted that the MedEconomics UK database quoted £14.50 as a fee for completing a simplistic post-market surveillance form for a pharmaceutical company.

The Panel was concerned about the material; participants did not know that it was activity undertaken on behalf of a pharmaceutical company to whom their details and the information provided would be disclosed. Nonetheless the material was not such as to constitute disguised promotion of a specific medicine and the Panel was thus obliged to rule no breach of Clause 10.2 of the Code.

Complaint received **25 April 2005**

Case completed **19 August 2005**

CASE AUTH/1714/5/05

ANONYMOUS EMPLOYEE v ASTRAZENECA

Call rates

An anonymous employee of AstraZeneca complained about the level of face-to-face contacts that the company had imposed on its representatives, and provided a copy of 'Campaign Notes Psychiatry Schizophrenia September 2004'.

The complainant referred to the campaign notes and submitted that AstraZeneca's demands were not only wholly unrealistic, but also grossly contravened the Code in terms of over-calling on any one customer. Representatives had to see 90% of customers 16 times a year, 12 times face-to-face and 4 times at meetings (as clearly stated in the campaign notes), and were incentivised to do so. In effect, the sales force was incentivised to break the Code. Failure to hit the 90% target also affected their pay review and any chances of promotion as it was a key performance indicator. In order to hit the target, representatives ended up hanging around corridors just to 'bump into' these people. This devalued their role and placed the industry in a bad light.

The complainant stated that if one raised this with AstraZeneca, it would not make any difference and would be a career-limiting move. If AstraZeneca was imposing such targets, the complainant failed to see how it could remain in the ABPI.

The Panel noted that the introductory paragraph to the campaign notes at issue highlighted the words 'No 1', 'Teamwork', 'coverage', 'frequency' and 'opportunities'. On the facing page a table detailed activity targets: on each day in quarters 1-4 representatives were expected to have four face-to-face calls with senior doctors. Daily activity rates were also given for meetings with senior doctors, certain nurses, pharmacists and junior doctors giving a total of 10 contacts per day. A table overleaf detailed coverage and frequency for priority 1 customers and stated that expected coverage was 90%; in each quarter there were to be 3 face-to-face meetings and one meeting with each of these customers. There was no differentiation made between unsolicited calls and calls made at the request of the customer. Although the coverage and frequency chart referred to 'customers' and so might include nurses and pharmacists, the Panel considered that at least some, if not the majority, of priority 1 customers would be doctors. The Panel noted that AstraZeneca expected its representatives to see 90% of the priority 1 customers in face-to-face meetings, not group meetings, 12 times a year ie once a month. Three of these meetings in the year could be unsolicited but in order to comply with the requirements of the Code the other 9 had to be requested by the doctor. The Panel queried how many doctors would truly request nine calls a year from a representative and considered that to achieve their target call rate representatives would possibly have to solicit requests to call.

The Panel noted that the campaign notes had not given any details about the requirements of the Code nor had the reader been referred to the Code. However, regardless of any reference to the Code and its requirements, the Panel considered that in setting the activity targets so high the campaign notes advocated a course of action which would be likely to lead to a breach of the Code. Representatives were incentivized to achieve the target coverage and frequency – the closer they were to target the greater the reward. The Panel noted AstraZeneca had acknowledged that there might have been activity out of line with the supplementary information to the Code. This would be a consequence of following the campaign notes. Thus the Panel ruled a breach of the Code. The Panel considered that AstraZeneca had not maintained high standards and a breach of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code.

An anonymous employee of AstraZeneca complained about the level of face-to-face contacts the company was imposing on its representatives. A copy of 'Campaign Notes Psychiatry Schizophrenia September 2004' was sent with the complaint.

COMPLAINT

The complainant stated that when the September 2004 psychiatry campaign notes were issued, the sales force had approximately 65 doctors to call on: 20 priority 1s which were concerned largely with general adults and 40 priority 2s which were concerned with the elderly and forensic and learning disabilities. Although the numbers of doctors had changed slightly since, they were very similar. The complainant submitted that AstraZeneca's demands were wholly unrealistic, and grossly contravened the Code in terms of over-calling on any one customer. Due to the structure of the territories in the psychiatry division, any one customer was called upon by two representatives: one selling Seroquel for schizophrenia and the other selling it for its bipolar indication. Depending upon the customer's business potential, there could be more AstraZeneca personnel trying to sell to them.

The complainant stated that AstraZeneca would not address the call rate/face-to-face element of the representative's work. Representatives had to see 90% of customers 16 times a year, 12 times face-to-face and 4 times at meetings (as clearly stated in the psychiatry campaign notes), and were incentivised to do so via the AstraZeneca AZpiration scheme whereby when they hit their activity targets they were awarded points which could be exchanged for gifts, holidays and goods. In effect, the sales force was incentivised to break the Code. Further, when representatives had their twice-yearly appraisals, the activity figures shown in the psychiatry campaign notes were assessed and if they did not hit the 90% target, thus breaching the Code, this automatically affected their pay review and any chances of promotion as it was a key performance indicator. The complainant submitted that many AstraZeneca personnel seeing so few customers so many times was inappropriate however they had to hit the targets but many doctors would not or could not see

representatives so many times, so, to in order to hit the target, representatives ended up hanging around corridors just to 'bump into' these people. This devalued their role and placed the industry in a bad light.

The complainant stated that if one raised this with AstraZeneca, it would not make any difference and would be a career-limiting move. If AstraZeneca was imposing such targets, the complainant failed to see how it could remain in the ABPI.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 2, 9.1 and 15.4 of the Code.

RESPONSE

AstraZeneca stated that it recognised the need to adhere to all parts of the Code including that relating to calls made by representatives on doctors where the supplementary information recommended that the number of calls each year should not normally exceed three on average except in specified circumstances.

The psychiatry campaign notes were a briefing to the AstraZeneca psychiatry sales force to support the promotion of Seroquel. AstraZeneca acknowledged that this document did not clearly differentiate between unsolicited (cold) calls and calls made expressly at the request of the health professional.

Terms used in the document were:

- **Activities** – all interactions undertaken by a representative with respect to a customer, including ad hoc conversations, unless otherwise defined.
- **A meeting** – a discussion with one or a number of customers. This might take the form of a representative presentation, customer presentation or an exhibition.
- **Coverage** – the % of the company's predefined target list of customers who were seen by a representative within a defined period of time.
- **Frequency** – the number of face-to-face interactions where a detail was delivered, between a representative and a target customer within a defined period of time.
- **Face-to-face** interaction – both solicited and unsolicited representative visits to a customer

AstraZeneca stated that one of the key elements of Clause 15.4 was that the frequency, timing and duration of calls must not inconvenience the health professional. The result of research involving psychiatrists that had recently been visited by an AstraZeneca representative, conducted January-March 2004, was provided. The company used an independent agency and had no say as to which customers (n=100) were interviewed. The research showed that the majority of those known to have had Seroquel details thought the frequency of calls and the content to be about right. Overall customers perceived their interactions with AstraZeneca as favourable. Using a different data source AstraZeneca found that the number of calls remembered by the sample was similar for all the major companies in the therapeutic area.

AstraZeneca stated that its records did not adequately distinguish between unsolicited and solicited calls. Additionally, the company had interviewed several of its sales employees, who had indicated that some representatives might have exceeded an unsolicited call rate of three per year. Further, the documents used to tell the psychiatry sales force about the reward scheme did not include the statement 'Calls must adhere to ABPI Guidelines'. This statement was included in similar briefing materials for all other sales forces – for comparison AstraZeneca provided the document which was used with the oncology sales force.

AstraZeneca concluded therefore, that despite there being no evidence that the frequency, duration and timing of calls had inconvenienced health professionals it accepted that there might have been activity out of line with the requirements of the supplementary information to Clause 15.4. The company was clarifying the requirements of Clause 15.4 with its sales force, and addressing this issue.

AstraZeneca noted that the complainant had alleged that AstraZeneca had not maintained high standards at all times and had brought discredit upon or reduced confidence in the pharmaceutical industry. These allegations could be summarized as AstraZeneca: made demands which were wholly unrealistic; incentivized individuals to breach the Code and encouraged individuals to act in a way that devalued the representative's role and placed the industry in a bad light.

AstraZeneca was confident that the majority of the materials it had created and communicated were sufficient to ensure that employees understood that they were obliged to comply with the Code at all times. AstraZeneca held a two-day induction programme for all new members of staff, irrespective of their previous industry experience, which covered the Code, the AstraZeneca Sales and Marketing Code of Practice and the AstraZeneca Code of Conduct (the latter two documents referred to the Code). The ABPI Code of Practice presentation, given in the induction programme, specifically covered the requirements of the Code on call frequency through a flashcard activity and as an integral part of the presentation itself. All the flashcards were used and discussed. In addition to the induction programme, all new sales representatives participated in a skills training course. All representatives new to the industry also received specific training on the Code to support their preparation for the ABPI Examination.

AstraZeneca introduced a corporate governance website as a way to tell employees about policies and to ensure that they understood and signed-off such policies annually, each June. This site was updated regularly. Copies of the site as it was in June 2004, at the time of launch of the campaign notes at issue and in its current form were provided. There was a read, understand and sign-off process. As stated on the opening web page 'the sign-off is not optional; it is mandatory for every employee'. Line managers were responsible for ensuring that their respective teams had read, understood and signed-off the policies, giving further training where requested or indicated. The Codes for Information page showed the very

broad scope of the policies to be signed-off including the ABPI Code of Practice, Corporate Governance and Sales and Marketing policies.

AstraZeneca stated that it had a mechanism in place for raising any concerns about a possible breach of policy through a number of routes. All employees were able to ask questions through their line manager or the website.

AstraZeneca stated that as part of the introduction of its Corporate Governance policy in June 2004 all managers attended a compulsory briefing session, which included a presentation on the AstraZeneca Code of Sales and Marketing Practice. This presentation included a section on the requirements of the ABPI Code with respect to call frequency and the slides were given to the managers to brief their teams on Corporate Governance.

All AstraZeneca employees had an annual performance plan, reviewed formally twice a year. A template performance plan for the Seroquel sales team was provided. The front page of the plan clearly stated 'achieve high levels of compliance with all relevant codes'. This demonstrated that AstraZeneca put corporate governance high on the agenda for its employees. Within an individual's personal plan, the representatives were required to specifically target 100% adherence to the ABPI Code. Annual performance reviews were measured against the achievement opposite all defined objectives. Only 10% of the weighting was given to the metrics element of which coverage and frequency was one small part. Other constituents were fully listed within the performance template.

As with all sales and marketing organisations AstraZeneca motivated its representatives with rewards. However, the company was aware of the special nature of its products and the customer base and this was reflected in its motivation and reward structure. Only a small element was based on coverage and frequency.

In addition to all of the above, ongoing training and coaching of the representatives covered how a representative closed an interaction with the customer, including confirmation of the points and actions discussed, which allowed the customer to indicate when they required a return visit.

AstraZeneca stated that it supported its representatives in the achievement of their coverage and frequency targets, through a variety of means, including reply paid cards, which offered a range of moderate items, appropriate to the role of a health professional. If requested, a representative would deliver the item and this was classed as a solicited visit, and would count towards coverage and frequency targets.

The complaint also raised issues around an individual's promotion being dictated by coverage and frequency achievements. AstraZeneca stated that it was not possible for a representative to be promoted on the basis of coverage and frequency. There were strict guidelines for promotion based on sales against target, capabilities and their performance review. Coverage and frequency did not feature within these guidelines. Furthermore, AstraZeneca had specific examples of individuals who had achieved a poor coverage and frequency rating but had been promoted based on the company's accepted criteria.

In conclusion, and in response to the allegations made, AstraZeneca submitted that the targets it set its representatives were not unrealistic. Individuals were not incentivised to breach the Code, and the company considered that its emphasis on corporate governance clearly set the expectation of ethical conduct at all times, and did not place the industry in a bad light.

AstraZeneca did not consider that it had breached Clause 9.1 of the Code, and that there was no evidence to support a breach of Clause 2.

Taking all the points and evidence above AstraZeneca accepted a breach of Clause 15.4 of the Code but denied breaches of Clauses 9.1 and 2.

AstraZeneca stated that corporate governance and ethical standards were high on the agenda for the whole company. It was the everyday responsibility of all employees and was not negotiable. AstraZeneca prepared its representatives to engage in quality interactions with the customers. Customer feedback was generally good with no specific complaints about call frequency. AstraZeneca motivated all its employees through means including rewards. The sales team were no exception. However, the components of the reward structure were not disproportionate to sales and were affected to a very small degree by coverage and frequency.

PANEL RULING

The Panel noted that the introductory paragraph to the psychiatry campaign notes at issue highlighted the words 'No 1', 'Teamwork', 'coverage', 'frequency' and 'opportunities'. On the facing page a table detailed activity targets: on each day in quarters 1-4 representatives were expected to have four face-to-face calls with senior doctors. Daily activity rates were also given for meetings with senior doctors, certain nurses, pharmacists and junior doctors giving a total of 10 contacts per day. A table overleaf detailed coverage and frequency for priority 1 customers and stated that expected coverage was 90%; in each quarter there were to be three face-to-face meetings and one meeting with each of these customers. There was no differentiation made between cold calls ie unsolicited calls and calls made at the request of the customer. Although the coverage and frequency chart referred to 'customers' and so might include nurses and pharmacists, the Panel considered that at least some, if not the majority, of priority 1 customers would be doctors. The complainant referred to 20 priority 1 doctors and 40 priority 2 doctors. The supplementary information to Clause 15.4 of the Code referred in detail to calls on doctors stating that a representative should not normally call upon a doctor more than three times a year on average. This did not include attendance at group meetings, a visit requested by the doctor or a visit to follow up a report of an adverse reaction. The Panel noted that AstraZeneca expected its representatives to see 90% of the priority 1 customers in face-to-face meetings, not group

meetings, 12 times a year ie once a month. Three of these meetings in the year could be cold calls but in order to comply with the requirements of the Code the other nine had to be requested by the doctor. The Panel queried how many doctors would truly request nine calls a year from a representative and considered that to achieve their target call rate representatives would possibly have to solicit requests to call. The Panel noted AstraZeneca's submission that it supported its representatives in the achievement of their coverage and frequency targets through a variety of means including reply paid cards with the possibility of representatives delivering requested items. Nonetheless, the Panel queried whether it was appropriate to give representatives targets to meet objectives over which the Panel considered they should have little influence and noted that representatives should not use the delivery of an item as an inducement to gain an interview. The Panel could understand why, as described by the complainant, representatives might hang around corridors in the hope of bumping into some of their priority customers so that they could record a face-to-face meeting which contributed to their set target.

The Panel noted that the campaign notes had not given any details about the requirements of the Code nor had the reader been referred to the Code. However, regardless of any reference to the Code and its requirements, the Panel considered that in setting the activity targets so high the campaign notes advocated a course of action which would be likely to lead to a breach of the Code. Representatives were incentivized to achieve the target coverage and frequency – the closer they were to target the greater the reward. The Panel noted AstraZeneca had acknowledged that there might have been activity out of line with the supplementary information to Clause 15.4 of the Code. This would be a consequence of following the campaign notes. Thus the Panel ruled a breach of Clause 15.4. The Panel considered that AstraZeneca had not maintained high standards. A breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure.

Complaint received **23 May 2005**

Case completed **30 June 2005**

CASE AUTH/1715/6/05

HOSPITAL CONSULTANT v CEPHALON

Actiq presentation

A consultant in pain management alleged that a presentation by a Cephalon representative about Actiq (oral transmucosal fentanyl citrate) was not balanced. Actiq was indicated for the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain but the complainant noted that in his presentation the representative cited the case of one patient who did not have cancer and received Actiq for the treatment of chronic pain with a very good result. The complainant considered that it was inappropriate for the representative to promote Actiq for an unlicensed indication.

The Panel noted that during the presentation the representative had been asked which patients were suitable for treatment with Actiq. The representative had stated that Actiq was specifically for patients with breakthrough pain in cancer. The Panel noted that although the representative was prompted to refer to the use of Actiq in areas that were known to him it considered that in reply he should only have referred to situations that were covered by the licensed indication. It appeared that there had been no direct question about the original licensed indication for Actiq nor about its use in chronic pain.

Actiq was licensed in the UK in October 2000 for the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic pain. In early 2002 however, pursuant to the mutual recognition procedure, the indication was changed to the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain. By referring to its past and present use in breakthrough pain in chronic pain the representative had promoted Actiq for a use which was inconsistent with the indication now given in the summary of product characteristics (SPC). Breaches of the Code were ruled.

The Panel considered that the prepared presentation entitled 'Break Through Pain in Cancer' was not unreasonable in terms of the licensed indication. It appeared that the complainant had not been misled as to the licensed indication for Actiq. While noting its rulings above, the Panel nonetheless ruled no breach of the Code.

A consultant in pain management complained about a presentation by a representative of Cephalon UK Limited about Actiq (oral transmucosal fentanyl citrate). Actiq was indicated for the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain.

COMPLAINT

The complainant was concerned that the representative's presentation was not balanced, for example he discussed clinical practice in a local area and cited the case of one patient who did not have cancer and received Actiq for the treatment of chronic pain. Apparently this patient had a very good result. The complainant considered that it was inappropriate for the representative to promote Actiq on the back of anecdotal evidence from one clinician about one patient, and although consultant medical staff might be sceptical about the implications of this, the presentation was directed to a wide range of health professionals and health assistants who would not critically appraise the information delivered in this manner compared with the research based PowerPoint presentation. The anecdotal information about the patient clearly promoted the product for an unlicensed indication.

The complainant also stated that the representative presented conflicting information; although he explicitly stated that Actiq should be used in the treatment of cancer pain, he also stated that it was used in the treatment of chronic pain. The representative explained that in Europe Cephalon had sought a product licence for chronic pain but because most of the research was in cancer pain one country would allow Actiq to be promoted only for cancer pain and it was on this basis that the product was licensed. The representative suggested that Actiq could be used outside of cancer pain, and was being used outside of cancer pain successfully. The complainant considered that this was inappropriate and outwith of the summary of product characteristics (SPC).

When writing to Cephalon, the Authority asked it to respond in relation to Clauses 3.2, 7.2 and 15.2 of the Code.

RESPONSE

Cephalon stated that at the lunchtime meeting the representative had used the slide presentation entitled 'Breakthrough Pain in Cancer'. Slide 16 outlined the licensed indication ie management of breakthrough pain in cancer where the background pain was stabilised on around the clock opioid therapy. Discussions arose during this slide and the audience raised several questions including which patient types were suitable for Actiq? The representative responded by stating that Actiq was for a specific group of patients with breakthrough pain in cancer. Examples of use highlighted were incident pain, management of patients undergoing outpatient palliative radiotherapy and management of painful wound dressings in cancer patients. It was during this question and answer session that the representative mentioned that one reason for interest among pain specialists in some of these areas was that Actiq had been initially licensed in the UK for breakthrough pain in chronic pain. However, subsequent to this UK approval the indication was changed during the Mutual Recognition Procedure. The representative again reminded the audience of the current licensed indication for Actiq. The representative mentioned the original indication of Actiq to explain why there was still an interest among the pain specialists in using Actiq in areas that were previously licensed indications.

Cephalon stressed that the meeting (including as to who would attend) was organised at the explicit request of one of the consultants for the whole pain

management team. The meeting was attended by four consultants, one specialist registrar, two pain clinical nurse specialists, one staff nurse, one psychologist, three health assistants and a senior occupational therapist. It was well recognised that each member of the team played a pivotal role in the management of patients suffering with chronic cancer pain and that their specific roles within the team were well defined. As only physicians were allowed to prescribe Actiq and in view of the fair and accurate content of the presentation Cephalon considered that the presentation made to the team was very balanced and indeed appropriate. As such the company did not accept that this was in breach of Clause 7.2.

Cephalon stated that the single case of a patient being treated for an unlicensed indication was mentioned during the questions and discussions whereby the representative was asked about the clinical situations where Actiq was being used. The questions and discussions were such that the representative was prompted also to mention the use of Actiq in areas that were known to him. In order to do this he qualified his comments by reiterating the licensed indication of Actiq as acknowledged by the complainant.

Cephalon submitted that it was acknowledged by the Code and member companies that representatives might be asked questions about unlicensed uses of their company's medicines and that it was reasonable for the representatives to know about the unlicensed uses of the medicines they promoted. In such situations, ie when prompted, representatives could respond to the specific question, provided they made it clear that it was an unlicensed use and that they referred the enquiry to the company's medical information department for a response. Cephalon provided a copy of its standard operating procedure 'Provision of Information regarding Unlicensed Indications', which was in line with the Code and on which all representatives had been trained.

Cephalon was confident that its representative had responded appropriately to the questions raised although it would have been preferable if he had not referred to the unlicensed use. However given the situation and nature of questions put to him and the fact that he followed this with a clear reminder as to what the authorized licensed indication for Actiq was, the company considered that under the circumstances the response was appropriate and that on balance the representative did not promote outside the licensed indication. In responding appropriately the representative had maintained high standards of ethical conduct. The company denied breaches of Clauses 3.2 and 15.2.

Cephalon noted the second observation that although the representative explicitly stated that Actiq was licensed for chronic cancer pain, he also stated that it was being used in the treatment of chronic pain (ie non-cancer pain). The complainant had stated that in this regard, the representative tried to explain in detail the licensing rationale behind the chronic pain indication within Europe and in doing so suggested that Actiq could be used in non-cancer patients.

Cephalon noted that Actiq was approved in the UK in October 2000 for the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic pain. Following this original approval in the UK via a National Licensing Procedure, the company sought to file for approval across Europe via the Mutual Recognition Procedure. This was successful although the indication was changed from 'chronic pain' to 'chronic cancer pain', to read: 'Management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain'. As such, Actiq was approved in the UK for the management of 'chronic pain' for about 18 months and a number of physicians were still aware of this.

Cephalon deeply regretted that there had been a misunderstanding between both parties during these discussions and considered that on this occasion, there was no case to answer. The company did not agree that its representative had promoted Actiq outside its licensed indication, thus there was no breach of Clause 3.2.

PANEL RULING

The Panel noted that during the course of the presentation the representative had been asked which patients were suitable for treatment with Actiq. The representative had stated that Actiq was specifically for patients with breakthrough pain in cancer. The Panel noted that although the representative was prompted to refer to the use of Actiq in areas that were known to him it considered that in reply he should have only referred to situations that were covered by the licensed indication. It appeared that there had been no direct question about the original licensed indication for Actiq nor about its use in chronic pain. By referring to its past and present use in breakthrough pain in chronic pain the representative had promoted Actiq for a use which was inconsistent with the indication now listed in the SPC. Breaches of Clauses 3.2 and 15.2 were ruled.

The Panel considered that the prepared presentation entitled 'Break Through Pain in Cancer' was not unreasonable in terms of the licensed indication. It appeared that the complainant had not been misled as to the licensed indication for Actiq. While noting its rulings above, the Panel nonetheless ruled no breach of Clause 7.2 of the Code.

During its consideration of this case, the Panel noted that an Actiq leavepiece 'Using Actiq: A step-by-step guide' (ref ACT 988/May 05) did not clearly state the licensed indication. A sub-heading on page 2 stated 'The goal for treating breakthrough pain with Actiq is …'. Smaller print on the same page referred both to opioid naïve, non-cancer patients as well as patients with breakthrough pain in cancer. Given that breakthrough pain in chronic pain was the original licensed indication for Actiq it was essential that doctors were told that the licence was now more restricted. The Panel was concerned that the leavepiece was not sufficiently clear about the licensed indication of the product and might lead to inappropriate prescribing. The Panel asked that Cephalon be advised of its concerns in this regard.

Complaint received **6 June 2005**

Case completed **19 July 2005**

GENERAL PRACTITIONER v RECKITT BENCKISER HEALTHCARE and BRITANNIA

Promotion of Gaviscon Advance

A general practitioner complained that the switch to Gaviscon Advance (sodium alginate and potassium bicarbonate), from the recently withdrawn Gaviscon, was being promoted by Reckitt Benckiser Healthcare and Britannia as being cost neutral to the NHS. This was based on a comparison of recommended 'cost per dose' but was not substantiated by any research. Since Gaviscon Advance had been available for many years the complainant was sure that the companies must have data which would show that it was not cost neutral. The complainant queried if NHS costs would increase as patients were likely to take the same dose as with original Gaviscon. The complainant further noted that the word 'upgrade' was used in a patient leaflet which suggested that Gaviscon Advance was superior. This was again misleading and unsubstantiated as no comparative data between Gaviscon and Gaviscon Advance was produced.

The complainant also noted that in the absence of the practice manager a representative was asked to leave a message. The receptionist was told that Gaviscon would no longer be available as of 'tomorrow', that 'the prescribing bureau were happy with a change to Gaviscon Advance' and finally that Gaviscon Advance was 'better' than Gaviscon. The complainant spoke to his local prescribing adviser who refuted that Gaviscon Advance had been endorsed by any local committee. The prescribing adviser also stated that other practices had received similar misleading telephone calls.

The Panel noted that the cost of a dose (5-10ml) of Gaviscon Advance (5.4-10.8p) was identical to that of Gaviscon (10-20ml) albeit that the dose volume was halved. The Panel could understand that some patients, used to taking 10-20ml of Gaviscon, might continue to take the same volume of Gaviscon Advance, thus doubling the cost of therapy. Nonetheless, the Panel noted that the materials at issue, which were aimed at health professionals, were very clear that the dose volume was less with Gaviscon Advance than with Gaviscon Liquid and that on a dose-for-dose basis the cost of the two treatments was the same. A 250ml bottle had been introduced so that the minimum acquisition cost was also the same. The Panel did not consider that the materials were misleading in that regard. No breach of the Code was ruled.

The patient leaflet and a template patient letter, both headed 'Your usual medication has been changed', informed the reader that their doctor had 'upgraded' their usual prescription such that instead of Gaviscon they were having Gaviscon Advance. Both explained that Gaviscon Advance was more concentrated, so that the dose volume would be less, that it contained less sodium and was slightly thicker in texture than Gaviscon. The Panel considered that the materials adequately described the advantages of Gaviscon Advance over Gaviscon so as to substantiate the use of the word 'upgrade'; the materials were not misleading in that regard. No breach of the Code was ruled.

The complainant had stated that he was happy for the companies to respond to his allegation about what the representative said to the receptionist as a general point. The representatives' briefing material instructed representatives to speak firstly to the practice manager or if they were unavailable, the lead GP. No reference was made to other surgery staff. The Panel noted the complainant's submission that having contacted the surgery, and in the absence of the practice manager, the representative was asked to leave a message with the receptionist. The briefing material discussed a mailing (the patient/practice education pack), switching from Gaviscon to Gaviscon Advance and stated that Gaviscon would be withdrawn from 4 June. The complainant's letter was dated 2 June, the day that the representative called, and so it was possible that the receptionist got the impression that Gaviscon would be no longer available 'as of tomorrow'. There was, however, no reference to Gaviscon Advance being endorsed by any local prescribing committee. The Panel noted the companies' submission that they were unable to respond without further details of the practice etc. In such circumstances it was impossible to determine where the truth lay. The Panel was thus obliged to rule no breach of the Code on this point.

A general practitioner complained about the promotion of Gaviscon Advance (sodium alginate and potassium bicarbonate) by Reckitt Benckiser Healthcare (UK) Limited and Britannia Pharmaceuticals Limited. Gaviscon had recently been withdrawn and replaced by Gaviscon Advance. The materials at issue were a product withdrawal information letter dated 24 May 2005, a frequently asked questions document which was attached to the withdrawal letter, a patient letter template, a tear-off patient leaflet pad and a single page leaflet which featured a table of further information about Gaviscon Advance which were provided to GPs in a mailing delivered on 25 May.

COMPLAINT

The complainant noted that the material suggested that Gaviscon Advance was cost neutral to the NHS. This was based on a comparison of recommended 'cost per dose' but was not substantiated by any research. Since Gaviscon Advance had been on the market for many years the complainant was sure that the companies must have field data costs which would demonstrate that Gaviscon Advance was not cost neutral. The complainant queried if costs would increase to the NHS as patients were likely to take the same dose as with original Gaviscon.

The complainant further noted that the word 'upgrade' was used in the patient leaflet which suggested that Gaviscon Advance was superior. This was again misleading and unsubstantiated as no comparative data between Gaviscon and Gaviscon Advance was produced.

The complainant also stated that in the absence of the practice manager the representative was asked to leave a message. The receptionist was told that Gaviscon would no longer be available as of 'tomorrow', that 'the prescribing bureau was happy with a change to Gaviscon Advance' and finally that Gaviscon Advance was 'better' than Gaviscon. The complainant spoke to his local prescribing adviser who refuted that Gaviscon Advance had been endorsed by any local committee. The prescribing adviser also stated that other practices had received similar misleading telephone calls.

Following a request from the Authority for further details the complainant stated that his complaint was not directed at an individual representative as he considered that companies were responsible for the actions of their staff. The complainant was happy for the companies to respond to this allegation as a general point.

The complainant considered that the discontinuation of Gaviscon on prescription was merely an attempt to increase profits for the company and thus the costs to the NHS; Gaviscon in its original formulation was available over-the-counter.

When writing to the companies to inform them of the complaint, the Authority requested that they consider the requirements of Clauses 7.2, 7.3, 7.4, 15.2 and 15.9 of the Code.

RESPONSE

Reckitt Benckiser and Britannia submitted identical responses. The complainant had considered that the materials at issue were misleading because they stated that dose for dose Gaviscon Advance was cost neutral with respect to Gaviscon. The cost for a dose of Gaviscon (10-20ml) was 5.4p to 10.8p. The cost for the equivalent dose of Gaviscon Advance (5-10ml) was 5.4 to 10.8p. The cost for Gaviscon Advance Tablets (1-2 tablets) was 5.4p to 10.8p. The companies were unclear how this data could be interpreted in any other way than showing cost neutrality on a dose for dose basis. If the complainant was concerned about the unit acquisition cost (a 500ml bottle of Gaviscon Advance was twice the cost of a 500ml bottle of Gaviscon) this was addressed by the introduction of a 250ml bottle of Gaviscon Advance at the same cost as a 500ml bottle of Gaviscon. The new presentation was clearly shown in the materials.

The companies noted the complainant's reference to 'field data costs' and his contention that the field costs would increase with Gaviscon Advance. The companies stated that they made no claims regarding so called field data as they had no such data; they considered that as stated in the supplementary information to Clause 7.2 of the Code, the best presentation of cost was on a dose for dose basis. The companies noted that the complainant feared that Gaviscon Advance could be given at the incorrect dose but stated that, as with all medicines, dosage instructions were clear in the summary of product characteristics (SPC), labelling and prescribing information. However, the companies had anticipated this concern and in order to try to prevent incorrect dosing they had provided reminder items for GPs, pharmacists and patients that for those patients switched from Gaviscon to Gaviscon Advance the dose should be halved. The companies did not consider that they were able to legislate further for those cases where the correct dose was ignored.

The companies did not accept that the word 'upgrade', defined in the dictionary as a rise in status, was misleading in respect of switching patients from Gaviscon to Gaviscon Advance. This term had been used for a number of years in communications with both health professionals and patients when switching from Gaviscon to Gaviscon Advance. 'Upgrade' was used because compared with Gaviscon Gaviscon Advance had less sodium, greater raft strength, a longer lasting raft and, because of the double concentration, the dose of Gaviscon Advance was half that of Gaviscon. These advantages were clearly stated in the materials. In addition to the stated advantages, Gaviscon Advance complied with the latest recommendations of the British National Formulary on sodium bicarbonate in dyspepsia treatment. The companies noted that the patient pad and template letter were provided as service items only. The prescriber was not compelled to use these items if they did not agree with their content.

The companies were concerned to learn of the telephone conversation between the practice receptionist and the representative. Both companies had a policy to comply with the Code and to this end, their representatives had been specifically trained on the materials about the withdrawal of Gaviscon that had been sent to GPs, Primary Care Trusts, pharmacists and hospitals. The companies monitored the performance of the field force and had very little negative feedback all of which had been followed up. The companies would welcome the opportunity to investigate this conversation further. However, this was not possible without the details of the complainant's practice and the date on which the conversation took place.

The training document that was used in training the representatives for discussions regarding the withdrawal of Gaviscon was provided.

PANEL RULING

The Panel noted that the cost of a dose (5-10ml) of Gaviscon Advance (5.4-10.8p) was identical to that of Gaviscon (10-20ml) albeit that the dose volume was halved. The Panel could understand that some patients, used to taking 10-20ml of Gaviscon, might continue to take the same volume of Gaviscon Advance, thus doubling the cost of therapy. Nonetheless, the Panel noted that the materials at issue, which were aimed at health professionals, were very clear that the dose volume was less with Gaviscon Advance than with Gaviscon and that on a

dose-for-dose basis the cost of the two treatments was the same. A 250ml bottle had been introduced so that the minimum acquisition cost was also the same. The Panel did not consider that the materials were misleading in that regard. No breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

The patient leaflet and the template patient letter, both headed 'Your usual medication has been changed' informed the reader that their doctor had 'upgraded' their usual prescription such that instead of Gaviscon they were having Gaviscon Advance. The leaflet and the letter went on to explain that Gaviscon Advance was more concentrated, so that the dose volume would be less, that it contained less sodium and was slightly thicker in texture than Gaviscon. The Panel considered that the materials adequately described the advantages of Gaviscon Advance over Gaviscon so as to substantiate the use of the word 'upgrade'; the materials were not misleading in that regard. No breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

The Panel noted that the complainant had stated that he was happy for the companies to respond to his allegation about what the representative said to the receptionist as a general point. The representatives' briefing material comprised a single page document headed 'PHM – Ideal GP Script' which instructed representatives to speak firstly to the practice manager or if they were unavailable, the lead GP. No reference was made to other surgery staff. The Panel noted the complainant's submission that having contacted the surgery, and in the absence of the practice manager, the representative was asked to leave a message with the receptionist. The script discussed a mailing (the patient/practice education pack) and switching from Gaviscon to Gaviscon Advance. The script stated that Gaviscon would be withdrawn from June 4 2005. The complainant's letter was dated June 2, the day that the representative called, and so it was possible that the receptionist got the impression that Gaviscon would be no longer available 'as of tomorrow'. There was, however, no reference to Gaviscon Advance being endorsed by any local prescribing committee. The Panel noted the companies' submission that they were unable to respond without further details of the practice etc. In such circumstances it was impossible to determine where the truth lay. The Panel was thus obliged to rule no breach of Clauses 15.2 and 15.9 of on this point.

Complaint received **7 June 2005**

Cases completed **28 July 2005**

GENERAL PRACTITIONERS v ASTELLAS

Regional advisory board meetings

Three general practitioners complained separately about invitations to attend regional advisory board meetings arranged by Yamanouchi (now known as Astellas). According to the agenda sent with the invitations the meetings were to look at the local management of overactive bladder (OAB) and incontinence in primary care, to discuss the solifenacin (Vesicare) data package, examine key messages for communication and to look at areas for support/educational needs.

In Case AUTH/1720/6/05 the complainant explained that all four partners at his practice had received an invitation; he alleged that the arrangements appeared to be a thinly disguised generous financial inducement to have the company's medicine promoted to the attending doctors. (The complainant drew attention to the honorarium of £200 which was offered).

In Case AUTH/1721/6/05 the complainant stated that he felt very uncomfortable when he and several of his partners received the invitation offering an honorarium merely to attend a meeting, presumably to promote the company's product.

In Case AUTH/1722/6/05 the complainant was concerned that the invitation and the enclosed programme could represent a marketing strategy with quite a substantial financial incentive for GPs to attend that did not fit with ABPI recommendations on interactions between doctors and the pharmaceutical industry.

The Panel noted that the complainants had not attended the meetings in question, the complaints had been made on the basis of the invitation sent by Astellas and the Panel made its ruling on this basis. The Panel did not consider that it had a complaint about the acceptability of the meetings *per se*.

The Panel noted that the invitation headed 'Yamanouchi OAB Regional Advisory Board for GPs…' stated that management of OAB varied between PCTs and, to understand these variations the company wished to draw on the invitees' expertise and counsel. The company also sought input as to which aspects of data from a recent comparative study involving solifenacin would be of most relevance to invitees, including in respect of local management protocols and where applicable, formularies. An honorarium was offered for the invitees' input and counsel.

The attached agenda showed that the meeting, which began at 7pm, was preceded by a hot buffet at 6.30pm. Local management of OAB and incontinence in primary care was discussed at 7.10pm for one hour followed by a 15 minute presentation and discussion on the solifenacin data package. Areas for support were discussed at 8.45pm before the meeting closed at 9pm. The Panel noted the invitee selection criteria. The Panel also noted Astellas' submission that it was almost impossible to identify specific health professionals within a geographical area. Invitations were sent to partners and practices which had a reasonable number of OAB patients. In two areas the invitation was extended to practice nurses with a particular interest in OAB. The Panel noted Astellas' submission that the agency which handled the meetings used different versions of the correspondence at different times and the company did not have access to every variation.

The Panel noted that 55 slides detailed the solifenacin data package and latest comparative data. Thirty five of these slides detailed the STAR study, a comparison of solifenacin with tolterodine 4mg XL (Pharmacia's product Detrusitol) in the management of OAB. The Panel was concerned about the large amount of comparative data provided. The agenda indicated that the purpose of the subsequent session; key messages for communication, was to link the clinical data to local issues including PCT protocols. The primary effect would thus be to highlight where Vesicare could be used locally instead of Detrusitol rather than address the stated overall objective of the meeting.

The Panel was very concerned about the level of control exercised by the company over the invitations; it had not seen all versions issued by its agency but nonetheless remained responsible for them under the Code. The Panel queried whether the selection of delegates stood up to independent scrutiny. Eight meetings had been held and had included 157 delegates ie an average of 19-20 at each meeting. The number of delegates (n=33) at one meeting, however, appeared too high to allow each one to contribute meaningfully such as to justify the honorarium. The Panel noted that this was one of two meetings held in one area 'due to the unexpectedly large response'; 54 delegates in all. In the Panel's view the number and size of advisory board meetings should be driven by the company's need not the willingness of potential delegates to attend. The Panel considered that the number and size of meetings was such that the scale of the activity was unacceptable. A large part of the clinical data presented at the meeting related to a comparison of Vesicare with a competitor. The Panel considered that offer of a payment to attend such a meeting amounted to an inducement contrary to the Code. High standards had not been maintained. Breaches of the Code were ruled. On balance the Panel did not consider that the arrangements as described on the invitations at issue brought discredit upon or reduced confidence in the pharmaceutical industry and no breach of Clause 2 was thus ruled.

The Panel noted the company's submission about the level of hospitality provided. The Panel did not consider the level of hospitality or venues as described on the invitations at issue to be inappropriate and no breach of the Code was ruled.

Three general practitioners complained about invitations to attend three different regional advisory board meetings arranged by Yamanouchi Pharma Ltd (now known as Astellas). According to the agenda

sent with the invitation the meetings were to look at the local management of overactive bladder (OAB) and incontinence in primary care, to discuss the solifenacin (Vesicare) data package, examine key messages for communication and to look at areas for support/educational needs.

COMPLAINTS

Case AUTH/1720/6/05 – The complainant explained that all four partners at his practice had received an invitation to attend a meeting at a local hotel. The complainant alleged that the arrangements appeared to be a thinly disguised generous financial inducement to have the company's medicine promoted to the attending doctors. (The complainant drew attention to the honorarium of £200 which was offered). If this invitation was sent to all practices in the area and to every GP within that practice indiscriminately, it was hardly a careful selection of suitable candidates to work on the advisory board.

Case AUTH/1721/6/05 – The complainant stated that he felt very uncomfortable when he and several of his partners received the invitation from Yamanouchi offering an honorarium merely to attend a meeting, presumably to promote the company's product. He would be interested as to whether this breached the Code.

Case AUTH/1722/6/05 – The complainant was concerned that the invitation and the enclosed programme could represent a marketing strategy with quite a substantial financial incentive for GPs to attend that did not fit with ABPI recommendations on interactions between doctors and the pharmaceutical industry.

Although this was supposedly some sort of interactive forum the enclosed programme appeared to focus primarily on presenting data about a particular product in the hope that people would then go on to prescribe it. Quite how potential attendees were selected the complainant was not entirely sure but he was a GP tutor and fairly well known in the local PCT and that might be how his name was put forward.

When writing to the company the Authority asked it to respond in relation to Clauses 2, 9.1, 18.1 and 19.1.

RESPONSE

Astellas stated that it had taken great care to ensure that the objectives and content of the meetings were clear from the letter and agenda enclosed with it and not in breach of the Code. However, from the complaints it appeared that the company's objectives had been misinterpreted.

Astellas explained that OAB was a common, chronic, distressing, debilitating, undignified condition which for the most part was managed in primary care. Market research carried out prior to the launch of Vesicare showed that management strategies varied widely across the country and indeed across regions and primary care trusts (PCTs).

As OAB was a new therapy area for Astellas the objective of these scientific meetings was for the company to understand the issues faced and the variations between regions and PCTs in terms of the management of OAB, local management protocols and formularies where applicable. Half of the meeting would be devoted to discussing local management of OAB and incontinence in primary care. This would then be followed by a presentation on the solifenacin data package in order that an interactive discussion to understand what, if any, of this information was important to local PCT protocols and practice could follow. However, at a couple of the meetings these two sessions overlapped and, with questioning from the delegates, took longer than initially anticipated. The meetings concluded with a discussion on local educational needs. Health professionals were expected to provide the company with input into these areas within their locality and as such were offered an honorarium of £200 for their time and counsel. Astellas did not consider that the fee paid for the 2 hour scientific meeting nor the level of hospitality was an inducement to prescribe, supply, administer or recommend solifenacin.

The letter explicitly informed the invitees that it was their counsel and input that was to be sought at the meeting. Delegates were expected and actively encouraged to participate in the discussions relating to OAB management within their geographical area, as with all other agenda items throughout the 2 hour evening meeting. No preparation was specifically requested of the health professionals prior to the meeting.

To ensure that the delegates would be able to give the requisite advice they were required to have an active role in management of OAB, using both medical and non-medical management and ideally with close working links with the local PCT.

In most cases it was almost impossible to identify specific health professionals within any given geographical area. Reference to market/IMS data helped to identify practices with a reasonable number of OAB patients. Hence the invitations were sent mainly to the listed partners within an identified practice and some other health professionals who were based in hospitals but who worked in primary care. By no means was this a large scale and indiscriminate mailing to health professionals within a given area, but one targeted as precisely as possible to ensure the greatest chance of including health professionals with the required experience and interest. In terms of how the delegates were chosen the success of the targeted approach used was highlighted by the fact that one of the complainants was a GP tutor who had a role within the PCT ie one of the key criteria for the meeting.

Astellas explained that this 2 hour scientific meeting was held in the evening, preceded by food and refreshments. All delegates were to receive £200 for their input and counsel (or £100 per hour) which the company submitted was not inconsistent with guidance received last year. There were ten additional meetings scheduled which had not been held at the time of receipt of the complaint; all ten had been cancelled.

Eight primary care meetings had taken place with 157 delegates attending. These meetings had taken place

in private hotel rooms in convenient hotels. Astellas provided the bills from six of these meetings marked to show how many delegates attended. The cost per head for hospitality for these venues had ranged from £13.93 to £29.32. This covered food, refreshments, wine and tea and coffee. The bills for the other two venues were awaited but were anticipated to be similar figures. There had been two meetings in one particular area due to an unexpectedly large response.

Delegates were offered travel expenses, covering standard rail tickets, taxis and car mileage. No flights were requested and accommodation was not offered as all the invitees were local to the meeting.

Astellas considered that the level of hospitality offered was appropriate for this type of meeting. The costs were not excessive (ranging from £13.93 to £29.32 per head from the 6 bills received) and were at a level which health professionals would have adopted if paying for themselves. Astellas therefore did not consider it was in breach of Clause 19.1.

As these were to be a series of scientific advisory board meetings, with attendees being paid for their expertise and input, Astellas denied a breach Clause 18.1 of the Code. No gift, benefit in kind or pecuniary advantage had been offered or given to members of the health professions as an inducement to prescribe, supply, administer or recommend solifenacin.

Apart from a form to claim the honorarium and expenses, no other material was given to the delegates at the meetings. Sample copies of the invitations and preliminary agendas and sample copies of correspondence sent to delegates for all eight meetings that had been held were provided. Although all original invitations mentioned that an honorarium would be paid only some stated the actual amount. Unfortunately the agency which handled the meetings used different versions of the correspondence at different times and the company did not have access to every variation, hence it provided sample letters sent out by the agency. Although inappropriate behaviour by the agency led to this problem Astellas recognised it was nevertheless responsible for the activities.

Astella was very concerned about the alleged breach of Clause 2 as it considered that there was nothing undertaken in this series of meetings that constituted bringing the industry into disrepute. The meetings were planned to provide the company with information on the local management of OAB, particularly as this was a new area for the company. The invitations were targeted to health professionals as accurately as possible. The level of hospitality was not out of proportion or excessive and the honorarium provided was reasonable. As such Astellas denied a breach of Clause 2 of the Code.

A copy of the presentation given at the initial meetings was provided. Some minor changes were made to this presentation as a result of the first two meetings such that a shorter similar version of the solifenacin data package was used for the remaining meetings.

PANEL RULING

The Panel noted that the complainants had not attended the meetings in question, the complaints had been made on the basis of the invitation sent by Astellas and the Panel made its ruling on this basis. The Panel did not consider that it had a complaint about the acceptability of the meetings *per se*.

The Panel considered that there was a difference between holding a meeting for health professionals and employing them to act as consultants. It was acceptable for companies to arrange advisory board meetings and the like and to pay health professionals and others for advice on subjects relevant to the products they promoted. Nonetheless the arrangements for such meetings had to comply with the Code. The requirements as to hospitality being of a reasonable standard etc, as set out in Clause 19 of the Code, had to be followed. The company must be able to justify the number of meetings held. The choice and number of delegates should stand up to independent scrutiny; each should be chosen according to their expertise such that they would be able to contribute meaningfully to the purpose and expected outcomes of the meeting. The number of delegates at a meeting should be limited so as to allow active participation by all. The agenda must allow sufficient time for feedback and input by the delegates. Invitations to participate in an advisory board meeting should clearly state the purpose of the meeting, the expected role of the invitees and the amount of work to be undertaken; it should be clear that any honorarium offered was a payment for such work and advice.

The proforma invitation headed 'Yamanouchi OAB Regional Advisory Board for GPs…' followed by the date began by explaining that management of OAB varied between PCTs and, to understand these variations the company wished to draw on the invitees' expertise and counsel. The invitation explained that the company also sought input as to which aspects of data from a recent comparative study involving solifenacin would be of most relevance to invitees, including in respect of local management protocols and where applicable, formularies. An honorarium was offered for the invitees' input and counsel.

The attached agenda showed that the meeting, which began at 7pm, was preceded by a hot buffet at 6.30pm. Local management of OAB and incontinence in primary care was discussed at 7.10pm for one hour followed by a 15 minute presentation and discussion on the solifenacin data package. Areas for support were discussed at 8.45pm before the meeting closed at 9pm. The Panel noted the invitee selection criteria. The Panel also noted Astellas' submission that it was almost impossible to identify specific health professionals within a geographical area. Invitations were sent to partners and practices which had a reasonable number of OAB patients. In two areas the invitation was extended to practice nurses with a particular interest in OAB. The Panel noted Astellas' submission that the agency which handled the meetings used different versions of the correspondence at different times and the company did not have access to every variation.

The Panel noted that of the 63 slides provided, 55 detailed the solifenacin data package and latest comparative data. Thirty five of these slides detailed the STAR study, a comparison of solifenacin with tolterodine 4mg XL (Pharmacia's product Detrusitol) in the management of OAB. The Panel was concerned about the large amount of comparative data provided. The agenda indicated that the purpose of the subsequent session; key messages for communication, was to link the clinical data to local issues including PCT protocols. The primary effect would thus be to highlight where Vesicare could be used locally instead of Detrusitol rather than address the stated overall objective of the meeting. The Panel further queried whether all of the clinical data which had been used at the initial meetings could be presented within the 15 minutes allocated although noted that the presentation had been shortened for future meetings.

The Panel was very concerned about the level of control exercised by the company over the invitations; it had not seen all versions issued by its agency but nonetheless remained responsible for them under the Code. The Panel queried whether the selection of delegates stood up to independent scrutiny. Eight meetings had been held and had included 157 delegates ie an average of 19-20 at each meeting. The number of delegates (n=33) at one meeting in particular, however, appeared too high to allow each one to contribute meaningfully such as to justify an honorarium of £200. The Panel noted that this was one of two meetings held in the same area 'due to the unexpectedly large response'; 54 delegates in all. In the Panel's view the number and size of advisory board meetings should be driven by the company's need not the willingness of potential delegates to attend. The Panel considered that the number and size of meetings was such that the scale of the activity was unacceptable. A large part of the clinical data presented at the meeting related to a comparison of Vesicare with a competitor. The Panel considered that offer of a payment to attend such a meeting amounted to an inducement contrary to requirements of Clause 18.1 of the Code. A breach of that clause was ruled accordingly. High standards had not been maintained; a breach of Clause 9.1 was ruled. On balance the Panel did not consider that the arrangements as described on the invitations at issue brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clause 2 was thus ruled.

The Panel noted the company's submission about the level of hospitality provided. The Panel did not consider the level of hospitality or venues as described on the invitations at issue to be inappropriate in relation to the requirements of Clause 19.1. No breach of that clause was ruled.

Complaints received:

Case AUTH/1720/6/05	**6 June 2005**
Case AUTH/1721/6/05	**8 June 2005**
Case AUTH/1722/6/05	**8 June 2005**
Cases completed	**22 August 2005**

PRIMARY CARE TRUST CLINICAL PHARMACISTS v RECKITT BENCKISER HEALTHCARE and BRITANNIA

Promotion of Gaviscon Advance

Two lead clinical pharmacists at an NHS primary care division complained about what a representative said during discussions about the withdrawal of Gaviscon Liquid and its replacement with Gaviscon Advance (sodium alginate and potassium bicarbonate). Gaviscon Advance was promoted jointly by Reckitt Benckiser Healthcare and Britannia.

The complainants stated that they had been told by Reckitt Benckiser that Gaviscon Liquid would be withdrawn. The accompanying literature from the company noted that practices would need to change to an alternative product and promoted the Gaviscon Advance range. The local prescribing bulletin had reminded prescribers that Gaviscon Advance was non formulary and that Peptac Liquid was a suitable formulary alternative to Gaviscon Liquid.

The complainants were concerned because they had received reports from three GP practices that a representative, during a telephone discussion about Gaviscon/Gaviscon Advance, had stated that Peptac liquid was soon to be discontinued and that the local medicines management/prescribing advisors supported switching all patients to Gaviscon Advance; neither of these statements were true. [In subsequent comments the complainants stated that one practice reported being told that Peptac was to be discontinued and that five practices had been told that Gaviscon Advance was approved for use locally].

The Panel noted that the complainants alleged that according to one local practice the representatives had stated, *inter alia*, that Peptac liquid was to be discontinued. The respondent companies did not know the identity of the GP practice at issue but knew the NHS region within which it was located. The Panel noted that the representatives in question could not confirm or deny making the statement at issue but considered that they had been misunderstood or misheard by the practices. The Panel considered that given the parties' differing accounts and that the concern had been raised by a single practice it was not possible to determine where the truth lay. The Panel was thus obliged to rule no breach of the Code.

The Panel noted that up to five practices had alleged that the representative(s) had incorrectly stated that the local medicines management prescribing advisers supported switching all patients to Gaviscon Advance. The Panel noted that the local prescribing bulletin reminded prescribers that Gaviscon Advance was non formulary and advised that Peptac liquid was a suitable formulary alternative. The Panel considered that, on the balance of probabilities, the weight of the evidence was such that the representative(s) had said, or otherwise implied, that the local advisers supported switching all patients to Gaviscon Advance and that was untrue; a breach of the Code was ruled. The representative(s) had not maintained a high ethical standard; a breach of the Code was ruled.

The Panel did not consider that the briefing material advocated a course of action which would lead to a breach of the Code.

Two lead clinical pharmacists at an NHS primary care division complained about statements a representative made about the withdrawal of Gaviscon Liquid. Gaviscon Liquid had recently been withdrawn and replaced with Gaviscon Advance (sodium alginate and potassium bicarbonate). Gaviscon Advance was promoted jointly by Reckitt Benckiser Healthcare (UK) Limited and Britannia Pharmaceuticals Limited.

COMPLAINT

The complainants stated that they had recently been told by Reckitt Benckiser that Gaviscon Liquid would be withdrawn as from 4 June. The accompanying literature from the company noted that practices would need to change to an alternative product and promoted the Gaviscon Advance range.

The official advice from the primary care division medicines management team was outlined in a bulletin sent to all practices on Friday, 27 May (an extract was provided). This reminded prescribers that Gaviscon Advance was non formulary and that Peptac Liquid was a suitable formulary alternative being therapeutically equivalent to Gaviscon Liquid and a lower cost.

The complainants had recently received reports from three GP practices that a representative of the company had telephoned them to discuss how they were handling the Gaviscon withdrawal and to promote Gaviscon Advance. The complainants were concerned because some information provided by the representative was not correct:

- 'Peptac liquid is soon to be discontinued' – Ivax, the manufacturer, had assured the complainants that it had no plans to discontinue the product.
- '[The local NHS primary care division] medicines management/prescribing advisers were supportive of switching all patients to Gaviscon Advance' – The medicines management team did not support a mass switch to this non formulary product.

When writing to the companies they were asked to respond in relation to Clauses 7.2, 15.2 and 15.9 of the Code.

RESPONSE

The companies submitted an identical responses to the complaint.

The companies explained that they took this matter very seriously and had interviewed the representatives in question about the complaint. The

representatives stated that they did not make the statements as alleged, but had stated that for those patients currently on peppermint Gaviscon Liquid, there was no peppermint flavoured Peptac and that the formulary did not exclude the use of Gaviscon Advance.

It was the companies' policy to operate within Code and they made every effort to ensure that the field force was appropriately trained in and complied with the Code. The representatives covering the local area were extremely experienced and fully trained in the materials used in the Gaviscon Liquid withdrawal. Both had over 10 years' experience and were well aware of the Code's requirements.

Although the companies had statements of the representatives involved they could not confirm or deny the alleged content of the conversations. However, they thought that the most likely explanation behind this complaint was that the representatives' message had been misunderstood or misheard by the recipient, but without full details of the incident the companies could not investigate the matter any further.

Copies of the material on which the representatives had been trained were provided.

FURTHER COMMENTS FROM THE COMPLAINANTS

The complainants explained that their complaint was based on the fact that five local independent GP practices had reported receiving a telephone call from a company representative asking them what they were doing about the imminent withdrawal of Gaviscon. During the conversation the representative promoted Gaviscon Advance as an alternative product. In all five practices the representative stated that the medicines management team/prescribing advisers supported switching patients to Gaviscon Advance. This statement was untrue.

In relation to the allegation about the discontinuation of Peptac liquid the complainants explained that in one case the practice manager had received the official medicines management team guidance that morning and so was surprised to hear conflicting information from the representative. When quoting that the medicines management team recommended switching patients to Peptac the representative criticised its sodium content and reported that it was soon to be discontinued. This statement was also untrue.

The complainants noted that the companies thought it likely that the representatives had been misunderstood or misheard. In relation to the view of the medicines management team, the complainants did not accept that five independent practices all misunderstood or misheard the same message. In relation to the position with Peptac, which was reported by one practice only, it was harder to know whether what was alleged was said or whether a misunderstanding had occurred.

PANEL RULING

The Panel noted that the parties' accounts differed. It was difficult in such circumstances to determine exactly what had transpired. The complainants alleged that according to one local practice the representatives had stated, *inter alia*, that Peptac liquid was to be discontinued. The respondent companies did not know the identity of the GP practice at issue but knew the NHS region within which it was located. The Panel noted that the representatives in question could not confirm or deny making the statement at issue but considered that they had been misunderstood or misheard by the practices. The Panel considered that given the parties' differing accounts and that the concern had been raised by a single practice it was not possible to determine where the truth lay. The Panel was thus obliged to rule no breach of Clauses 7.2, 15.2 and 15.9 of the Code.

The Panel noted that up to five practices had alleged that the representative(s) had incorrectly stated that the medicines management prescribing advisers supported switching all patients to Gaviscon Advance. The Panel noted that the local prescribing bulletin reminded prescribers that Gaviscon Advance was non formulary and advised that Peptac liquid was a suitable formulary alternative. The Panel considered that, on the balance of probabilities, the weight of the evidence was such that the representative(s) had said, or otherwise implied that the medicines management team supported switching all patients to Gaviscon Advance and that was untrue; a breach of Clause 7.2 was ruled. The representative(s) had not maintained a high ethical standard; a breach of Clause 15.2 was ruled.

The Panel did not consider that the briefing material advocated a course of action which would lead to a breach of the Code. No breach of Clause 15.9 was ruled.

Complaint received **10 June 2005**

Cases completed:
AUTH/1723/6/05 **22 August 2005**
AUTH/1724/6/05 **30 August 2005**

PRIMARY CARE TRUST CHIEF PHARMACIST and HEAD OF MEDICINES MANAGEMENT v RANBAXY

Mirtazapine letter

A chief pharmacist at a primary care trust (PCT) (Case AUTH/1727/6/05) and a head of medicines management at a PCT (Case AUTH/1732/6/05) each complained about a letter sent by Ranbaxy which discussed the cost savings achieved when changing from mirtazapine oro-dispersible (Zispin Soltab marketed by Organon) to generic mirtazapine film-coated tablets. The first paragraph of the letter began by thanking the recipient for responses and queries received pursuant to an earlier letter advising of the availability of mirtazapine film-coated tablets and concluded 'We would also like to thank you for the prescriptions'.

Both complainants noted that the unsolicited letters had been sent to officers of PCTs none of whom were medically qualified. The first paragraph of the letter was untrue; the recipients had not been in previous contact with Ranbaxy. The complainants noted that the letter offered the recipients samples of mirtazapine; breaches of the Code were alleged as mirtazapine was a prescription only medicine and the recipients were not health professionals. Both complainants queried the meaning of the phrase 'We would also like to thank you for the prescriptions'.

The Panel noted that each complainant stated that the letter was unsolicited and described the first paragraph as untrue. The Panel noted Ranbaxy's submission that it was a standard letter, intended for everyone involved in prescribing mirtazapine. The first paragraph implied that there had been some communication between the addressee and the company pursuant to an earlier letter announcing the availability of the product and in relation to the complainants' PCTs that was not so. The first paragraph was misleading in this regard. A breach of the Code was ruled.

The Panel noted that the Code provided that samples could only be provided to health professionals qualified to prescribe that product. The Panel noted that samples had been offered to three officers of two PCTs none of whom were health professionals. Therefore a breach of the Code was ruled. High standards had not been maintained. A breach of the Code was ruled.

A chief pharmacist at a primary care trust (PCT) (Case AUTH/1727/6/05) and a head of medicines management at a PCT (Case AUTH/1732/6/05) each complained about a letter sent by Ranbaxy (UK) Ltd which discussed the cost savings achieved when changing from mirtazapine oro-dispersible (Zispin Soltab marketed by Organon) to generic mirtazapine film-coated tablets. The first paragraph of the letter began by thanking the recipient for responses and queries received pursuant to an earlier letter advising of the availability of mirtazapine film-coated tablets and concluded 'We would also like to thank you for the prescriptions'.

Case AUTH/1727/6/05

COMPLAINT

The complainant explained that the letter was sent to the chief executive of the PCT who knew nothing about it, and had had no communication with Ranbaxy. The letter was therefore unsolicited and the first paragraph was not true. The complainant did not understand what 'We would also like to thank you for the prescriptions' meant.

The letter offered the chief executive some samples of this prescription only medicine. The complainant alleged a breach of Clause 17 of the Code which provided that 'A sample of a medicine may be provided only to a health professional qualified to prescribe that particular medicine'.

Case AUTH/1732/6/05

COMPLAINT

The complainant explained that the letter was sent to the lay chair of the PCT and to the chief executive who was not medically qualified. These letters were unsolicited and the first paragraph was not true. The complainant was fascinated how the phrase 'We would also like to thank you for the prescriptions' came to be in the letter and what it meant.

The letters also offered samples of a prescription only medicine. Clause 17 of the Code provided that 'A sample of a medicine may be provided only to a health professional qualified to prescribe that particular medicine'. Therefore this offer breached that clause.

When advising Ranbaxy of the complaints the Authority asked it to respond in relation to Clauses 7.2, 9.1 and 17.1 of the Code.

RESPONSE

Ranbaxy explained that the letter, sent out on 8 June, was a standard letter sent to all the PCTs in the country. When it was sent the company was not aware that the chief executive of the PCT was neither medically qualified nor a pharmacist; it intended to send the letter to a medically qualified person or a pharmacist.

The letter thanked the recipient for the queries and responses which had been received by the company. Since it was a standard letter, it was intended to address all people involved in prescribing mirtazapine. Furthermore, the queries and responses mentioned were primarily telephone queries which Ranbaxy had received in significant numbers enquiring about pack sizes, availability, etc.

The letter also thanked the recipient for the prescriptions. This again was directed not only at the chief executive of the PCT but at all relevant people involved in prescribing mirtazapine. A clear trend of increasing numbers of prescriptions for this product was based on an increase in the numbers of orders being received.

Since Ranbaxy was not aware that the chief executive was neither medically qualified nor a pharmacist, samples were offered. The primary reason for making this offer to the PCTs was to help them decide whether to recommend this product to be included in their GP formulary. Samples were often requested by pharmaceutical advisors at PCTs for identification purposes. To date no samples had been sent to any of the PCTs.

Based on the above explanation and since the chief executive was not medically qualified Ranbaxy accepted that the offer of samples was not appropriate as defined in Clause 17.1 of the Code, and the company sincerely apologized for any offence or inconvenience caused.

Ranbaxy was unclear as to why it had been asked to comment under Clause 7.2. The company presumed that this was for the economic comparison that it had detailed in the standard letter. The company did not accept that it was in breach of Clause 7.2 of the Code. The letter had provided a clear perspective of the basis of the comparison and the detail in the mailing was self explanatory. This was a standard letter sent out to all the PCTs and the economic claims in the letter applied nationally.

Ranbaxy could not understand why it had been asked to respond in relation to Clause 9.1 of the Code. The letter did not mention of any of the things which might be covered by the supplementary information to Clause 9.1 and Ranbaxy denied any breach under this clause. Ranbaxy endeavoured to maintain high standards at all times which was reflected clearly by the fact that it had never had any complaint under the Code until now.

In summary, Ranbaxy had not intended to send this mailing to people who were not medically qualified; its despatch to the chief executive of the PCT was an error for which the company apologized. As a corollary to this Ranbaxy would not offer samples to people who were not medically qualified. No samples had been sent out to date. The company always endeavoured to maintain high standards in its working practices. However, it would be reviewing its procedures.

PANEL RULING

The Panel noted that the letter at issue began by thanking the recipient for 'the responses and queries in response to our letter informing you of the availability of Mirtazapine film-coated tablets …' and thanked the addressee 'for the prescriptions'. The Panel noted that the chief executive of the PCT at issue in Case AUTH/1727/6/05 had had no previous communication with the company. Each complainant stated that the letter was unsolicited and described the first paragraph as untrue. The Panel noted Ranbaxy's submission that it was a standard letter, intended for everyone involved in prescribing mirtazapine. The first paragraph implied that there had been some communication between the addressee and the company pursuant to an earlier letter announcing the availability of the product and in relation to the complainants' PCTs that was not so. The first paragraph was misleading in this regard. A breach of Clause 7.2 was ruled.

The Panel noted that Clause 17.1 provided that samples could only be provided to health professionals qualified to prescribe that product. They must not be provided to administrative staff. The Panel noted that samples had been offered to three officers of two PCTs none of whom were health professionals. The Panel considered that Clause 17.1 covered the offer and provision of samples. A breach of Clause 17.1 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that it was a requirement of the Code that promotional material should only be sent to those people whose need for, or interest in, the particular information could reasonably be assumed; material for clinicians might not be appropriate for use with administrative staff. Companies must ensure that mailings etc are properly targeted so that they comply with the Code in this regard. The Panel was concerned that the letter at issue appeared to have been written on the basis of 'one size fits all' which was unacceptable. The Panel asked that Ranbaxy be advised of its concerns in this regard.

Complaints received:
Case AUTH/1727/6/05 **20 June 2005**
Case AUTH/1732/6/05 **24 June 2005**

Cases completed **12 August 2005**

CASE AUTH/1730/6/05

TAKEDA/DIRECTOR v GLAXOSMITHKLINE

Promotion of Avandamet

Takeda complained about the promotion of Avandamet (rosiglitazone/metformin) by GlaxoSmithKline. The items at issue were a hospital detail aid, a general practice detail aid, a stand alone flyer and two leavepieces.

As the complaint included an alleged breach of undertaking, that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

The claim 'Helps lower blood pressure…' was included in both detail aids and both leavepieces. The flyer included a closely similar claim ('helps lower patients blood pressure'). Takeda noted that in June 2004 GlaxoSmithKline was ruled in breach of the Code with regard to an Avandia and Avandamet journal advertisement on the basis that it implied that Avandia and Avandamet were indicated for blood pressure reduction which was not so. In July 2004, following another complaint about the same advertisement, GlaxoSmithKline was again ruled in breach of Clause 7.2, 'as the impression was given that Avandia and Avandamet were licensed for the reduction of blood pressure'.

The Avandamet summary of product characteristics (SPC) stated that it was licensed for the treatment of type 2 diabetes, particularly in overweight patients who were unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone. There was no mention of any blood pressure lowering effects in the SPC.

In addition to the claim that Avandamet helped lower blood pressure, additional claims regarding the two products were made such as: 'By restoring the vasodilatory action of insulin on endothelial cells, rosiglitazone allows blood vessels to dilate, thereby reducing blood pressure', 'Consistent and significant reductions in BP in patients with Type 2 diabetes on rosiglitazone' and 'Helps lower blood pressure, and thus has the potential to lower CV risk'.

In the hospital detail aid there was a page entitled 'By targeting insulin resistance, Avandamet helps lower blood pressure', below which there was a graph depicting the results from seven 'studies', two of which were double-blind, three were open, and two were observational/chart reviews.

Takeda discussed the methodology and outcome of Natali *et al* (2004), Honisett *et al* (2003) and Chiquette *et al* (2004) in relation to Avandamet lowering blood pressure.

In conclusion, Takeda alleged that any claims concerning the blood pressure lowering effects of Avandamet were not accurate, balanced, fair, objective, unambiguous, did not reflect the totality of the data and were outside the licensed indication. Takeda also alleged a breach of the Code in view of the lack of compliance with undertakings previously given, and a breach of Clause 2.

The Panel noted that the material now at issue was different to that at issue in Cases AUTH/1580/4/04 and AUTH/1590/5/04. The two previous cases had concerned journal advertisements which the Panel had considered gave undue emphasis to the reduction of blood pressure as a benefit of using Avandia and Avandamet. The advertisements had implied that the two products were licensed for blood pressure reduction which was not so.

Turning to the material now at issue the Panel noted that although each piece referred to blood pressure reduction it did not consider that this benefit of therapy was presented such as to suggest that the indication, or the prime reason to prescribe Avandia or Avandamet was to lower blood pressure as alleged. On balance no breach of the Code was ruled. The Panel did not consider that the material now at issue was sufficiently similar to the material at issue in the previous cases and there was no breach of the undertakings given in those cases. No breach of the Code was thus ruled.

Both detail aids and one leavepiece featured a bar chart entitled 'Consistent and significant reductions in BP in patients with Type 2 diabetes on rosiglitazone'. The seven bars depicted represented reductions in systolic blood pressure (SBP) ranging from 4mmHg to 12mmHg. The seven studies from which the results were taken were a mixture of designs – double blind, open and observational/chart review. The reduction in SBP in one study was not statistically significant although it was stated that the reduction in diastolic blood pressure (DBP) in that study was. Most of the reductions shown were from baseline except for two studies (Bakris *et al* 2003, Yosely *et al* 2004) which were against sulphonylureas. A meta-analysis published at the time that the material at issue was prepared (quarter 4 2004) (Chiquette *et al*) reported that five trials had shown no significant differences between rosiglitazone and placebo in changes in SBP or DBP.

The Panel noted that there was no detail on the bar chart as to the number of patients in each study, their baseline blood pressure or any other clinical characteristics. Although the bar chart, both from its title and its content, informed readers that rosiglitazone had demonstrated a consistent and significant blood pressure lowering effect the Panel noted the findings of Chiquette *et al* and was concerned that the bar chart did not represent the totality of the data in that regard. In any event the bar chart was not sufficiently detailed such as to allow a reader to judge the clinical significance of the results shown. It was impossible for a reader to know what magnitude of effect to expect. The Panel considered that overall the bar chart was misleading and that the claim for a consistent and significant blood pressure lowering effect could not be substantiated. Breaches of the Code were ruled.

The claim 'Avandamet delays disease progression' appeared in both detail aids and one leavepiece above a graph depicting change in HbA_{1c} over time.

In addition both leavepieces also included a closely similar claim, 'Delays disease progression by providing a sustained improvement in glycaemic control'.

Takeda stated that there was no evidence that Avandamet delayed the rate of progression of disease or reduced the complication of the disease. There was no end point data to support this claim.

Section 5.1 of the SPC for Avandamet stated 'In studies with a maximal duration of three years, rosiglitazone given once or twice daily in combination with metformin produced a sustained improvement in glycaemic control (FPG and HbA_{1c}). … An outcome study has not been completed with rosiglitazone, therefore the long-term benefits associated with improved glycaemic control of rosiglitazone have not been demonstrated. There are no studies completed assessing long-term cardiovascular outcomes in patients receiving rosiglitazone in combination with metformin.' The SPC was thus clear that the long-term benefits associated with improved glycaemic control had not been demonstrated.

The graph used to substantiate the claim showed the change in HbA_{1c} over time and was derived from an analysis of an open-label extension of two double-blind studies, each of 26 weeks' duration, with an aim to evaluate the efficacy of rosiglitazone in combination with metformin. Clearly only those patients who benefited from the earlier studies would have entered this open-label extension and so it related to a patient population biased in favour of Avandamet. For this reason alone no conclusions could be drawn concerning the efficacy of Avandamet in changing HbA_{1c} over time.

Furthermore Takeda noted that the daily dose of metformin used in this study was 2.5g which did not relate to any of the currently marketed dosage forms of Avandamet and was above the recommended dose in the Avandamet SPC.

Takeda alleged that the claim that 'Avandamet delays disease progression' was not accurate, balanced, fair, and objective, was ambiguous and was outside the licensed indication.

The Panel considered that the headline 'Avandamet delays disease progression' was wide ranging and had not been qualified even with the graph beneath it. Although GlaxoSmithKline had submitted that there were other ways in which Avandamet delayed disease progression some of these were due to the metformin component and not to the combination product Avandamet *per se*. In that regard the Panel noted the statement in the Avandamet SPC that 'There are no studies completed assessing long-term cardiovascular outcomes in patients receiving rosiglitazone in combination with metformin'. The Panel considered that overall the headline 'Avandamet delays disease progression' was a broad, unqualified claim that could not be substantiated in all aspects of its meaning. The claim was misleading in that regard. Breaches of the Code were ruled. The Panel did not consider that the claim was inconsistent with the particulars listed in the Avandamet SPC. The SPC referred to sustained improvement in glycaemic control and this was one aspect of delaying disease progression.

The Panel ruled no breach of the Code with regard to the claim 'Delays disease progression by providing a sustained improvement in glycaemic control' as the context was clear.

The claim 'Help improve patients' HDLc levels' appeared as a heading to a page of the hospital detail aid.

Takeda noted that Section 4.8 of the Avandamet SPC listed hyperlipidaemia and hypercholesterolaemia as uncommon disorders. Further on it also stated that in double-blind studies, hypercholesterolaemia occurred in 2.1% of patients treated with rosiglitazone and that the elevated total cholesterol levels were associated with an increase in LDLc and HDLc, but the ratio of total cholesterol:HDLc was unchanged or improved in long term studies. Overall these increases were generally mild to moderate and usually did not require discontinuation of treatment.

The promotional items did not refer to any of the other key lipid parameters recognised as independent risk factors for cardiovascular risk ie cholesterol, triglycerides or LDLc. Indeed the recently published NICE Guidelines for the 'Treatment of Type 2 diabetes, lipid management' stated in the section headed 'In the use of serum lipids to make treatment decisions' that 'Treatment recommendations are made on the basis of total cholesterol, LDL-cholesterol and triglycerides…there is not enough evidence to make recommendations for incorporating HDL-cholesterol levels for making recommendations on therapy'.

Takeda noted that the graph related to treatment with rosiglitazone 4-8mg and metformin 2.5g daily, ie an unlicensed dose of Avandamet, and that the bar chart referred to rosiglitazone 4-8mg alone.

In conclusion any claim that Avandamet could 'help improve patients HDLc levels' was not accurate, balanced, fair, objective, was ambiguous and was outside the licensed indication.

Takeda was also concerned that the claim suggested that Avandamet had a beneficial effect on a patient's lipid profile as a whole, which was not the case in view of its detrimental effects on cholesterol and triglycerides levels reported in the SPC, as well as in the analysis by Chiquette *et al*, referred to earlier, where rosiglitazone was shown to significantly increase LDLc and total cholesterol.

The Panel considered that the page at issue clearly related to Avandamet's effect on HDLc levels only. In that regard the claim at issue did not imply a beneficial effect on a patient's lipid profile overall. Nor did the Panel consider that the claim implied that HDLc levels were the only aspect of a patient's lipid profile that were important. The Panel considered that HDLc data had been presented merely as one cardiovascular risk factor that needed to be taken into account. The Panel noted that there was data to show that Avandamet helped to improve HDLc levels. The data depicted in the graph was effectively the results of therapy with up to the

maximum dose of Avandamet plus 500mg metformin. Metformin could be used as monotherapy or in combination with oral antidiabetic medicines. The maximum daily dose of metformin was 3g per day. The Panel considered that the claim was balanced objective, fair and unambiguous. The Panel did not consider that the claim was inconsistent with the particulars listed in the Avandamet SPC. No breach of the Code was ruled.

The claim 'Help reduce your patients' microalbuminuria' appeared as a page heading in the hospital detail aid.

Takeda noted that Section 4.4 of the Avandamet SPC, stated:

> **'As metformin is excreted by the kidney, serum creatinine concentrations should be determined regularly:**
>
> **– at least once a year in patients with normal renal function**
>
> **– at least four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly patients.**

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may be impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with an NSAID.'

The claim that Avandamet could 'Help reduce your patients' microalbuminuria' implied that it had renoprotective effects or benefits which was far from the case especially when such cautionary notes were included in the SPC. Takeda therefore advocated that such claims were irresponsible with respect to rationale and safe prescribing of medicines to patients for what was a long term, chronic condition. In addition Takeda noted that the data related to rosiglitazone 4mg and not to Avandamet.

The Panel noted that microalbuminuria was the earliest indicator of nephropathy attributable to diabetes. Left unchecked a patient could progress from having microalbuminuria to eventually having renal failure. The detail aid had previously featured the bold, unqualified headline 'Avandamet delays disease progression'. In that context the Panel considered that the claim 'Help reduce your patients' microalbuminuria' might be taken to imply some degree of renal protection and this was misleading.

The Panel noted that depicted on the page at issue was data showing that rosiglitazone monotherapy reduced the albumin:creatinine ratio by 26.4% at one year (n=57) and that 43% of patients (n=14) had microalbuminuria normalised at one year. There was no data shown for combination therapy with rosiglitazone plus metformin. In this regard the Panel considered that the page which featured the Avandamet product logo was misleading.

Overall the Panel considered that the page was misleading both due to the implication of the renal protection and the use of Avandia data in the context of the Avandamet logo. The claim that Avandamet 'Helps reduce your patients' microalbuminuria' could not be substantiated. Breaches of the Code were ruled. The Panel did not consider that the claim was inconsistent with the Avandamet SPC. No breach of the Code was ruled in that regard.

Takeda stated that throughout these pieces Avandia data had been used to support Avandamet claims (eg vascular inflammation, carotid IMT progression rate claims). There were also examples of use of data which used higher doses of the medicines than were recommended in the SPC.

'The maximum recommended daily dose of Avandamet is 8mg rosiglitazone plus 2000mg metformin hydrochloride.' The risk; benefit of a total daily dose of 8mg rosiglitazone plus 2500mg metformin had therefore not been established.

Furthermore, in accordance with agents in this class, patients commencing treatment with Avandamet needed to undergo careful dose titration, so that the optimal risk:benefit profile was established for each patient. There was no mention in these materials of the need for careful titration of Avandamet.

There were several occasions where the data used to support a claim was using a higher dosage of rosiglitazone than the Avandamet presentation (2mg/1000mg) promoted in the pieces.

The Panel noted the very general nature of the complaint and considered that aspects of it had already been ruled upon above. The Panel was concerned about the vagueness of the complaint and considered that Takeda should be advised that if it wanted to make specific allegations about specific claims then it should make another more detailed complaint.

With regard to the alleged failure to mention the need for careful titration of Avandamet, the Panel noted that the SPC stated that the usual starting dose of Avandamet was 4mg/day rosiglitazone plus 2000mg/day metformin. This could be increased. Dose titration with rosiglitazone (added to the optimal dose of metformin) might be considered before the patient was switched to Avandamet. In the circumstances the Panel did not consider that the materials were either inconsistent with the SPC or not capable of substantiation and thus ruled no breach of the Code.

Takeda stated that, in summary, it was concerned that GlaxoSmithKline had undertaken a major promotional campaign, targeting different health professionals and making a wide range of claims concerning Avandamet's 'beneficial effects' in patients with type 2 diabetes, which were outside the licence, misleading and could not be substantiated. The materials were also unbalanced as undue prominence was given to all these additional benefits and there was very little information concerning the primary indication for Avandamet; namely glycaemic control. Furthermore in the sales aids one might have expected to have seen data which depicted the safety/tolerability of the product especially as Avandamet was a black triangle product and so the risk:benefit profile of the

product was still under intensive review by the Committee on Safety of Medicines. Such activities could not be in the interest of either the patients or the pharmaceutical industry as a whole and hence Takeda alleged of a breach of Clause 2 of the Code.

Whilst noting its rulings above the Panel nonetheless did not consider that the matters considered were such as to justify a ruling of a breach of Clause 2 which was reserved as a sign of particular censure.

Takeda UK Limited complained about the promotion of Avandamet (rosiglitazone/metformin) by GlaxoSmithKline UK Ltd. The items at issue were a hospital detail aid (ref AVM/DAS/04/16690/1), a general practice detail aid (ref AVM/DAP/04/16691/1), a stand alone flyer (ref AVM/LVP/04/14823/1) and two leavepieces (refs AVM/OBH/17110/1 and AVM/LVP/04/16665/1). Takeda supplied Actos (pioglitazone). Both products were oral hypoglycaemics.

As the complaint included an allegation of a breach of undertaking, that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. In addition to those clauses cited by Takeda, GlaxoSmithKline was also asked to respond with regard to the requirements of Clause 9.1 of the Code.

1 Claim 'Helps lower blood pressure …'

This claim was included in both detail aids and both leavepieces. The flyer included a closely similar claim ('helps lower patients blood pressure').

COMPLAINT

Takeda noted that in June 2004 GlaxoSmithKline was ruled in breach of Clauses 3.2 and 7.2 of the Code with regard to an Avandia and Avandamet journal advertisement on the basis that it implied that Avandia and Avandamet were indicated for blood pressure reduction which was not so (Case AUTH/1580/4/04). In July 2004, following another complaint about the same advertisement, GlaxoSmithKline was again ruled in breach of Clause 7.2, 'as the impression was given that Avandia and Avandamet were licensed for the reduction of blood pressure' (Case AUTH/1590/4/04).

The Avandamet summary of product characteristics (SPC) stated that it was licensed for the treatment of type 2 diabetes, particularly in overweight patients who were unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone. There was no mention of any blood pressure lowering effects in the SPC.

In addition to the claim that Avandamet helped lower blood pressure, additional claims regarding the two products were also made such as: 'By restoring the vasodilatory action of insulin on endothelial cells, rosiglitazone allows blood vessels to dilate, thereby reducing blood pressure'; 'Consistent and significant reductions in BP in patients with Type 2 diabetes on rosiglitazone'; 'Helps lower blood pressure, and thus has the potential to lower CV risk'.

In the hospital detail aid there was a page entitled 'By targeting insulin resistance, Avandamet helps lower blood pressure', below which there was a graph depicting the results from seven 'studies', two of which were double-blind, three were open, and two were observational/chart reviews.

The first double-blind study (Natali *et al* 2004), 'Vascular effects of improving metabolic control with metformin or rosiglitazone in type 2 diabetes', aimed to test whether vascular reactivity was modified by improving metabolic control and peripheral resistance in type 2 diabetes. The study involved type 2 diabetics (n=74) randomised to rosiglitazone (8mg/day), metformin (1.5g/day) or placebo for 16 weeks. Insulin sensitivity, ambulatory blood pressure, and forearm blood flow were measured in response to: intra-arterial acetylcholine; intra-arterial nitroprusside; the clamp and blockade of nitric oxide. Following this test procedure it was found that the diastolic blood pressure (DBP) for those patients in the rosiglitazone group only fell by 2±1mmHg, $p<0.05$.

In terms of the validity and credibility of the study and thus any claims for Avandamet that could be made from it, Takeda noted that:

- all patients were normotensive at study entry,
- their change in DBP was as the result of a challenge to the various test agents listed above,
- the decrease in DBP was 2±1mmHg, so not only was it clinically irrelevant the confidence intervals were very wide,
- there was no prospectively defined hypothesis as to what statistically significant and clinically relevant blood pressure effects were being looked for, and indeed the study hypothesis was to look at vascular reactivity,
- no effect was seen on systolic blood pressure,
- the number of patients was too small to conclude anything about type 2 diabetics in general,
- none of the patients actually received Avandamet; they received the maximum dose of rosiglitazone (8mg) which was unachievable with the 2mg/1g Avandamet tablets as promoted in the sales aid,
- a proportion of patients were on concomitant ACE inhibitors which further confounded the results.

The second 'double-blind study' cited was a brief letter in the journal Diabetes Care, 'Rosiglitazone lowers blood pressure and increases arterial compliance in postmenopausal women with type 2 diabetes' (Honisett *et al*, 2003). This study involved 31 postmenopausal women with established diabetes who were randomised to receive either 4mg rosiglitazone (n=21) or matching placebo (n=10).

In terms of validity and scientific credibility of any claims for Avandamet that could be made, Takeda noted that:

- once again all the patients were normotensive at study entry (124/71mmHg),
- it was undertaken in postmenopausal women, and so a subset of type 2 diabetics,

- only 21 patients received rosiglitazone,
- eighty percent of women continued to take metformin, a sulphonylurea or both throughout the trial, so it was not known how many actually received Avandamet nor indeed what the blood pressure lowering effects were for this small subset of patients.

Furthermore a meta-analysis of all randomised controlled studies, of 12 weeks' duration or more, identified five which compared the effect of thiazolidinediones on cardiovascular risk factors (Chiquette *et al* 2004). On reviewing the studies for rosiglitazone, the authors concluded that 'No significant differences between rosiglitazone and placebo in changes in systolic or diastolic blood pressure were seen'.

In conclusion, any claims concerning the blood pressure lowering effects of Avandamet were not accurate, balanced, fair, objective, unambiguous, did not reflect the totality of the data and were outside the licensed indication in breach of Clauses 3.2, 7.2, 7.4. Takeda also alleged, in view of the lack of compliance with the undertakings given in respect of Cases AUTH/1580/4/04 and AUTH/1590/4/04, breaches of Clause 22 and Clause 2.

RESPONSE

GlaxoSmithKline noted that Cases AUTH/1580/4/04 and AUTH/1590/4/04 concerned an advertisement entitled 'Confront the new challenges for Type 2 diabetes', which was subsequently withdrawn following the Panel ruling. The Panel considered that 'the balance of the advertisement was such that undue emphasis had been given to the reduction of blood pressure as a benefit of using Avandia and Avandamet'. The Panel also stated that, 'whilst it was not [emphasis added] necessarily unacceptable to compare the blood pressure effect of sulphonylureas and rosiglitazone any such comparisons could only be made within the context of treating patients for the products' licensed indications'.

These conclusions were consistent with a letter received by GlaxoSmithKline in March 2004 from the Medicines and Healthcare products Regulatory Agency (MHRA). This stated that 'the glitazones may have a secondary effect on other parameters such as, modifying lipids and blood pressure …. All advertising referring to these effects should make it clear that these are secondary, to ensure that prescribers are not misled. In particular, claims for secondary effects should not be given equal prominence to the licensed indication'. The Panel ruled that undue emphasis was given to blood pressure as around 50% of the material concerned referred to the effects of rosiglitazone on blood pressure and the artwork was such that the average reader would be drawn selectively to this information.

In all of the materials at issue, the main body of text referred to the licensed use of rosiglitazone to treat type 2 diabetes. The materials referred to blood pressure lowering as a secondary effect mediated via insulin resistance as required by the MHRA. The data on glycaemic control was always referred to first and the blood pressure data was not given undue prominence – see the table below. As such these materials gave a balanced view of the effects of rosiglitazone on blood pressure, set in the context of the licensed indication of the lowering of blood glucose. Thus GlaxoSmithKline strongly refuted any breach of Clauses 9.1, 22 and 2 as alleged.

The importance of tight blood pressure control in the management of type 2 diabetes was well established. The UK prospective diabetes study (UKPDS) had confirmed that a 10/5mmHg reduction in blood pressure translated into a reduction in diabetes related endpoints of 24%. The HOT study confirmed the benefit of lowering blood pressure to a mean DBP of 82.6mmHg. The HOPE study confirmed the benefits of relatively modest blood pressure lowering, with a 1.9/3.3mmHg reduction in blood pressure translating into a reduction of 25% in cardiovascular events. In this context, blood pressure lowering was both important and clinically relevant in diabetes. Thus the secondary effects of Avandamet were relevant to clinicians treating type 2 diabetics.

Clause 3.2 of the Code stated that 'Promotion of a medicine must be in accordance with the terms of its marketing authorization …'. In all of GlaxoSmithKline's materials promotion was clearly in line with the marketing authorization for rosiglitazone. As shown above, taking blood pressure as the specific example, secondary effects were in the context of the indication and were given much less prominence.

The MHRA letter stated that 'glitazones may have a secondary effect on other parameters, such as modifying blood lipids and blood pressure …'. In the ruling in Case AUTH/1590/5/04, it was stated that 'The Panel had noted that there was evidence showing a beneficial effect of Avandia on blood pressure in Type 2 diabetics …'. The Panel also stated that 'whilst it was not [emphasis added] necessarily unacceptable to compare the blood pressure effect of sulphonylureas and rosiglitazone any such comparisons could only be made within the context of treating patients for the products' licensed indications'. Therefore the materials were not in breach of Clause 3.2.

With regard to Takeda's comments about Natali *et al*, GlaxoSmithKline noted that in that study reduction in 24hr ambulatory blood pressure was –4/2mmHg ($p<0.05$) versus baseline. Changes versus placebo were larger, at –5/4mmHg. The text stated that 24hr ambulatory monitoring took place prior to test procedures, contrary to Takeda's assertion. In any case, both sodium nitroprusside and acetylcholine had very short half-lives and no more than a few minutes' effect on blood pressure. Certainly, GlaxoSmithKline was not aware of any evidence that they had any relevant effect on 24hr blood pressure when used for assessment of endothelial function.

Honisett *et al* was a randomised double-blind study to examine the effects of rosiglitazone on blood pressure. Honisett *et al* had confirmed that antihypertensive medication remained stable during this study, demonstrating its validity as a blood pressure lowering trial. Indeed, there was a highly statistically

significant reduction in blood pressure of 12/6mmHg in the rosiglitazone treated group.

With reference to Takeda's assertion that Chiquette *et al* demonstrated no significant effect of rosiglitazone on blood pressure, GlaxoSmithKline noted that the search criteria ruled out abstracted data, a significant body of which pointed towards blood pressure lowering effects of rosiglitazone.

In assessing whether a breach of Clause 7.2 had occurred it was essential to examine the whole evidence base. Examining the range of studies in the graph it was easy to see that despite variations in study methodology, duration and design the results showed a consistent effect. There was now evidence from at least 14 studies with over 12,000 patients which had shown a consistent blood pressure lowering effect.

Three review articles, (Bakris *et al* 2003, Greenberg 2003 and Viberti 2003) cited in GlaxoSmithKline's original response to Case AUTH/1580/4/04 also supported blood pressure lowering effects of thiazolidinediones. To quote from Greenberg, 'Thiazolidinedione therapy has significant effects on the traditional elements of the metabolic syndrome, including dyslipidaemia and hypertension'.

Since publication of these materials Ambery *et al* (2005) had published an evidence review, 'Treatment of hyperglycaemia with rosiglitazone therapy is associated with clinically meaningful reductions in systemic blood pressure', of 12 studies which demonstrated the blood pressure lowering effects of rosiglitazone. Blood pressure lowering effects of up to 20/17mmHg were seen in studies reviewed for this analysis. Two further randomised controlled studies had demonstrated positive effects on blood pressure in large patient numbers (Bakris *et al* 2005 and Home *et al* 2004). Whilst this review itself could not retrospectively support the claims made, the data were known to GlaxoSmithKline and awaiting publication.

In summary, the balance of the materials was not weighted in favour of blood pressure and there was a broad and robust evidence base for the blood pressure lowering effects of rosiglitazone. GlaxoSmithKline considered that there had been no breach of Clauses 3.2, 7.2 and 7.4 and no breach of undertaking.

PANEL RULING

The Panel noted that the material now at issue was different to that at issue in Cases AUTH/1580/4/04 and AUTH/1590/5/04. The two previous cases had concerned journal advertisements which the Panel had considered had given undue emphasis to the reduction of blood pressure as a benefit of using Avandia and Avandamet. The advertisements had implied that the two products were licensed for blood pressure reduction which was not so. Breaches of the Code had been ruled.

Turning to the material now at issue the Panel noted that although each piece referred to blood pressure reduction it did not consider that this benefit of therapy was presented such as to suggest that the indication, or the prime reason to prescribe Avandia or Avandamet, was to lower blood pressure as alleged. On balance no breach of Clauses 3.2 and 7.2 was ruled.

The Panel did not consider that the material now at issue was sufficiently similar to the material at issue in either Case AUTH/1580/4/04 or Case AUTH/1590/5/04 and there was no breach of the undertakings given in those cases. No breach of Clauses 2, 9.1 and 22 was thus ruled.

Both detail aids and also one leavepiece (ref AVM/LVP/04/16665/1) featured a bar chart entitled 'Consistent and significant reductions in BP in patients with Type 2 diabetes on rosiglitazone'. The seven bars depicted represented reductions in SBP ranging from 4mmHg to 12mmHg. The seven studies from which the results were taken were a mixture of designs – double blind, open and observational/chart review. The reduction in SBP in one study was not statistically significant although it was stated that the reduction in DBP in that study was. Most of the reductions shown were from baseline except for two studies (Bakris *et al* 2003, Yosely *et al* 2004) which were against sulphonylureas. A meta-analysis published at the time that the material at issue was prepared (quarter 4 2004) (Chiquette *et al*) reported that five trials had shown no significant differences between rosiglitazone and placebo in changes in SBP or DBP.

The Panel noted that there was no detail on the bar chart as to the number of patients in each study, their baseline blood pressure or any other clinical characteristics. Although the bar chart, both from its title and its content, informed readers that rosiglitazone had demonstrated a consistent and significant blood pressure lowering effect the Panel noted the findings of Chiquette *et al* and was concerned that the bar chart did not represent the totality of the data in that regard. In any event the bar chart was not sufficiently detailed such as to allow a reader to judge the clinical significance of the results shown. It was impossible for a reader to know what magnitude of effect to expect. The Panel considered that overall the bar chart was misleading and that the claim for a consistent and significant blood pressure lowering effect could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

2 Claim 'Avandamet delays disease progression'

This claim appeared in both detail aids and the leavepiece (ref AVM/LVP/04/16665/1) above a graph depicting change in HbA_{1c} over time. In addition both leavepieces also included a closely similar claim, 'Delays disease progression by providing a sustained improvement in glycaemic control'.

COMPLAINT

Takeda stated that there was no evidence that Avandamet delayed the rate of progression of disease or reduced the complication of the disease. There was no end point data to support this claim for Avandamet.

Section 5.1 of the SPC for Avandamet stated 'In studies with a maximal duration of three years,

rosiglitazone given once or twice daily in combination with metformin produced a sustained improvement in glycaemic control (FPG and HbA_{1c}). ….An outcome study has not been completed with rosiglitazone, therefore the long-term benefits associated with improved glycaemic control of rosiglitazone have not been demonstrated. There are no studies completed assessing long-term cardiovascular outcomes in patients receiving rosiglitazone in combination with metformin.' The SPC was thus clear that the long-term benefits associated with improved glycaemic control had not been demonstrated.

Takeda noted that Section 4.8 of the SPC Undesirable effects, Metabolism and nutrition disorders, listed 'diabetes mellitus aggravated' as being an uncommon, undesirable effect.

Takeda noted that the graph used to substantiate the claim showed the change in HbA_{1c} over time, the reference for which was a poster abstract whose authors gave their location as GlaxoSmithKline UK Ltd. The graph was derived from an analysis of an open-label extension of two double-blind studies, each of 26 weeks' duration, with an aim to evaluate the efficacy of rosiglitazone in combination with metformin. Clearly only those patients who benefited from the earlier studies would have entered this open-label extension and so it related to a patient population biased in favour of Avandamet. For this reason alone no conclusions could be drawn concerning the efficacy of Avandamet in changing HbA_{1c} over time, and in any case the main objectives of such studies were to determine the long-term safety and tolerability of a product not its long-term efficacy.

Furthermore Takeda noted that the daily dose of metformin used in this study was 2.5g which did not relate to any of the currently marketed dosage forms of Avandamet and was above the recommended dose in the Avandamet SPC.

In conclusion the claim that 'Avandamet delays disease progression' was not accurate, balanced, fair, and objective, was ambiguous and was outside the licensed indication and so in breach of Clauses 3.2, 7.2, and 7.4.

RESPONSE

GlaxoSmithKline stated that disease progression in the context of a chronic disease might be defined as any or all of the following: delayed progression of underlying pathophysiological processes or prevention of worsening of primary clinical manifestations of disease; delayed progression of other associated clinical abnormalities; delayed or reduced need for additional medication or intervention and delay or reduction in incidence of long-term complications and/or their underlying causal factors.

- Delayed progression of underlying pathophysiological processes and worsening of primary clinical manifestation of the disease (rosiglitazone in monotherapy or in combination): Improvements in insulin sensitivity, improvements in beta cell function, sustained improvement in glycaemic control.
  - Jariwala *et al* (2003), Nadra *et al* (2004) and Fonseca *et al* (2000) had demonstrated improvements in blood glucose, insulin resistance and beta cell function in type 2 diabetics.
  - An Avandamet study (Stewart *et al* 2005) demonstrated a 24.8% improvement in insulin sensitivity, and a 14% improvement in beta cell function.
  - The Avandamet SPC stated 'In studies with a maximal duration of three years, rosiglitazone given once or twice daily in combination with metformin produced a sustained improvement in glycaemic control (fasting plasma glucose and HbA_{1c})'.
  - The RECORD 18 month interim analysis of rosiglitazone and metformin in combination had demonstrated a reduction in HbA_{1c} of –0.60% (baseline 7.84%). (Home *et al* 2004).
  - Ovale *et al* (2004), in a study of rosiglitazone in combination with metformin and sulphonylurea demonstrated restoration of first phase insulin response (a key component of adequate beta cell function) after commencement of rosiglitazone.
  - Smith *et al* (2004), in a monotherapy study of rosiglitazone demonstrated improvements in the proinsulin:insulin ratio, a key indicator of beta cell health.
- Delayed progression of other associated clinical abnormalities: Positive data on blood pressure, lipids, microalbuminuria, inflammatory markers.
  - Extensive positive data existed for the effects of rosiglitazone on blood pressure (as detailed above).
  - Two studies (Bakris *et al* 2003 and Bakris 2005) supported positive effects of rosiglitazone on microalbuminuria.
  - A number of studies currently existed demonstrating positive effects of rosiglitazone on HDL cholesterol.
  - A number of studies had also demonstrated positive effects of rosiglitazone on C-reactive protein.
- Delayed or reduced need for additional medicine or intervention: time to additional therapy/ initiation of insulin.
  - A real-life epidemiological study conducted in patients soon after launch of rosiglitazone supported the hypothesis that metformin and rosiglitazone in combination delayed the initiation of insulin (Koro *et al* 2004).
- Delay or reduction in long-term complications: reduction in in-stent re-stenosis for rosiglitazone. Metformin (Avandamet SPC – effect on cardiovascular outcomes).
  - Choi *et al* (2004) suggested a significant reduction in the rate of in-stent restenosis in type 2 diabetics taking rosiglitazone monotherapy. In-stent restenosis was related to vascular inflammation (a cause of atherosclerosis). Reduction of inflammatory markers by rosiglitazone was

thought to be responsible for the reduction in restenosis seen in this study.

– With regard to the effects of metformin on disease progression in terms of cardiovascular outcomes the Avandamet SPC stated:

  'The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

  – a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034

  – a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017

  – a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021)

  – a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years (p=0.01).'

Evidently these various facets of the disease were linked. Thus, it was because of Avandamet's effects on the underlying pathophysiology that the primary clinical manifestation (blood glucose) and associated abnormalities were delayed/improved. This in turn reduced the need for further intervention. Thus the claim of delayed disease progression was supported by a consistent and multifactorial set of data that was relevant to the primary indication.

In summary, there was evidence across a range of pathologies associated with type 2 diabetes to support effects of rosiglitazone and metformin in combination on disease progression. GlaxoSmithKline denied the alleged breaches of Clauses 3.2, 7.2 and 7.4 in relation to claims that Avandamet delayed disease progression.

As noted by Takeda, the dose of metformin used was 2.5g. As stated in the European Public Assessment Report (EPAR) for Avandamet, the dose of metformin administered was 2.5g in the studies considered. No clinical studies were considered necessary as the fixed dose combination was considered bioequivalent to the components. However the EPAR stated that for the fixed dose combination, the maximum dose of metformin was 2g daily. This differed from the dose in the clinical studies (2.5g). However it was noted, that as there was little clinical benefit from increasing the dose above 2g, the efficacy of Avandamet with 2g of metformin had been demonstrated sufficiently based on the submitted doses.

As this formed the basis of the regulatory approval for Avandamet, its use as described was completely appropriate.

PANEL RULING

The Panel noted GlaxoSmithKline's submission that disease progression in terms of diabetes could be defined as any or all of a number of parameters. One of these parameters was the sustained improvement in glycaemic control. The Panel considered, however, that the headline 'Avandamet delays disease progression' was wide ranging and had not been qualified even with the graph beneath it. Although GlaxoSmithKline had submitted that there were other ways in which Avandamet delayed disease progression some of these were due to the metformin component and not to the combination product Avandamet *per se*. In that regard the Panel noted the statement in the Avandamet SPC that 'There are no studies completed assessing long-term cardiovascular outcomes in patients receiving rosiglitazone in combination with metformin'. The Panel considered that overall the headline 'Avandamet delays disease progression' was a broad, unqualified claim that could not be substantiated in all aspects of its meaning. The claim was misleading in that regard. Breaches of Clauses 7.2 and 7.4 were ruled. The Panel did not consider that the claim was inconsistent with the particulars listed in the Avandamet SPC. The SPC referred to sustained improvement in glycaemic control and this was one aspect of delaying disease progression. No breach of Clause 3.2 was ruled.

The Panel ruled no breach of Clauses 7.2, 7.4 and 3.2 of the Code with regard to the claim 'Delays disease progression by providing a sustained improvement in glycaemic control' as the context was clear.

3 Claim 'Help improve patients' HDLc levels'

This claim appeared as a heading to a page of the hospital detail aid.

COMPLAINT

Takeda noted that Section 4.8 of the Avandamet SPC Undesirable side effects, listed hyperlipidaemia and hypercholesterolaemia as uncommon disorders. Further on in this section it also stated that in double-blind studies, hypercholesterolaemia occurred in 2.1% of patients treated with rosiglitazone and that the elevated total cholesterol levels were associated with an increase in LDLc and HDLc, but the ratio of total cholesterol:HDLc was unchanged or improved in long term studies. Overall these increases were generally mild to moderate and usually did not require discontinuation of treatment.

The promotional items did not refer to any of the other key lipid parameters recognised as independent risk factors for cardiovascular risk ie cholesterol, triglycerides or LDLc. Indeed the recently published NICE Guidelines for the 'Treatment of Type 2 diabetes, lipid management' stated in the section headed 'In the use of serum lipids to make treatment decisions' that 'Treatment recommendations are made on the basis of total cholesterol, LDL-cholesterol and

triglycerides…there is not enough evidence to make recommendations for incorporating HDL-cholesterol levels for making recommendations on therapy'.

In trying to substantiate the above claim Takeda noted that the graph related to treatment with rosiglitazone 4-8mg and metformin 2.5g daily, ie an unlicensed dose of Avandamet, and that the bar chart referred to rosiglitazone 4-8mg alone.

In conclusion any claim that Avandamet could 'help improve patients HDLc levels' was not accurate, balanced, fair, objective, was ambiguous and was outside the licensed indication in breach of Clauses 3.2, 7.2, and 7.4.

Takeda was also concerned that the claim suggested that Avandamet had a beneficial effect on a patient's lipid profile as a whole, which was not the case in view of its detrimental effects on cholesterol and triglycerides levels reported in the SPC, as well as in the analysis by Chiquette *et al*, referred to earlier, where rosiglitazone was shown to significantly increase LDLc and total cholesterol.

RESPONSE

GlaxoSmithKline stated that raised levels of HDLc were recognised as early as 1977 (Framingham study) as being protective against coronary heart disease. Both the Helsinki Heart Study and VAHIT studies provided strong evidence for beneficial effects of raising HDLc. Both studies used gemfibrozil 1.2g, and resulted in increases in HDLc of between 6 and 11%. In the VAHIT study, a rise of 6% in HDLc resulted in a reduction in outcomes of 22%.

In contrast, it had been suggested that raised triglycerides were not associated with increased cardiovascular risk. Analyses of the Helsinki Heart study and the UKPDS 23 failed to demonstrate a relationship between raised triglyceride levels and increased cardiovascular events.

Fonseca *et al* (2000) and Gomez-Perez *et al* (2002) (combination rosiglitazone and metformin studies), indicated rises in HDLc of between 10 and 13%. A large number of other studies also existed to support positive effects of rosiglitazone on HDLc.

Statins were well-recognised as the gold-standard therapy for LDLc lowering and a number of studies such as the CARDS study supported outcome benefits related to LDLc lowering by these agents. There were however secondary beneficial effects of rosiglitazone on LDL particle size when used in conjunction with statins.

HDLc lowering effects of rosiglitazone were beneficial secondary effects. As such, it was made clear in materials that the primary effects of rosiglitazone therapy were in blood glucose lowering, in line with the licensed indication. There was no reference to any other lipid effects and therefore no inference that Avandamet had a beneficial effect on a patient's lipid profile as a whole. In addition these effects were only mentioned in a detail aid intended only for secondary care physicians who would find this information relevant and be able to contextualise it in the context of type 2 diabetes. As such GlaxoSmithKline refuted the claim of breaches in Clauses 3.2, 7.2 and 7.4.

PANEL RULING

The Panel considered that the page at issue clearly related to Avandamet's effect on HDLc levels only. In that regard the claim at issue did not imply a beneficial effect on a patient's lipid profile overall. Nor did the Panel consider that the claim implied that HDLc levels were the only aspect of a patient's lipid profile that were important. The Panel considered that HDLc data had been presented merely as one cardiovascular risk factor that needed to be taken into account. The Panel noted that there was data to show that Avandamet helped to improve HDLc levels. The data depicted in the graph was effectively the results of therapy with up to the maximum dose of Avandamet plus 500mg metformin. Metformin could be used as monotherapy or in combination with oral antidiabetic medicines. The maximum daily dose of metformin was 3g per day. The Panel considered that the claim was balanced objective, fair and unambiguous. No breach of Clauses 7.2 and 7.4 was ruled. The Panel did not consider that the claim was inconsistent with the particulars listed in the Avandamet SPC. No breach of Clause 3.2 was ruled.

4 Claim 'Help reduce your patients' microalbuminuria'

This claim only appeared as a page heading in the hospital detail aid.

COMPLAINT

Takeda noted that Section 4.4 of the Avandamet SPC, Special warnings and special precautions for use, stated:

> 'As metformin is excreted by the kidney, serum creatinine concentrations should be determined regularly:
>
> – at least once a year in patients with normal renal function
>
> – at least four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly patients.
>
> Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may be impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with an NSAID.'

The claim that Avandamet could 'Help reduce your patients' microalbuminuria' implied that it had renoprotective effects or benefits which was far from the case especially when such cautionary notes were included in the SPC. Takeda therefore advocated that such claims were irresponsible with respect to rationale and safe prescribing of medicines to patients for what was a long term, chronic condition.

In addition Takeda noted that the data related to rosiglitazone 4mg and not to Avandamet.

In conclusion the claim that Avandamet could 'help reduce your patients' microalbuminuria' was not accurate, balanced, fair, objective, was ambiguous and was outside the licensed indication and so in breach of Clauses 3.2, 7.2, and 7.4. It also had implications

with respect to rational prescribing and the patient's safety.

RESPONSE

GlaxoSmithKline stated that microalbuminuria was a very early manifestation of changes in kidney function related to diabetes and referred to the leakage of small amounts of protein into the urine. This was in marked contrast to decreased creatinine clearance and raised serum creatinine. These were manifestations of renal failure which occurred late in the disease and were contra-indications to metformin therapy.

GlaxoSmithKline was therefore surprised at the misinterpretation by Takeda of microalbuminuria equalling decreased creatinine clearance and raised serum creatinine. It was irresponsible of Takeda to suggest that all medicines with a contra-indication of raised serum creatinine should be excluded in patients with even early diabetic nephropathy, the sign of which was of course microalbuminuria. This would preclude use of ACE-inhibitors and angiotensin-II receptor blockers (including Candesartan marketed by Takeda), these two classes of medicine had shown reno-protective attributes when used in diabetic nephropathy.

Diabetic nephropathy was indeed a long-term chronic condition and as such, provided a large window for possible early intervention. The NICE guidance entitled 'Management of Type 2 Diabetes – Renal disease, prevention and early management' supported this view.

The document stated, 'Microalbuminuria is the earliest indicator of renal disease (nephropathy) attributable to diabetes'.

This view was supported by the Oxford Handbook of Endocrinology and Diabetes which stated that microalbuminuria occurred some 5-15 years after the diagnosis of type 1 diabetes and might be present at diagnosis of type 2 diabetes. It went on to state that deterioration of glomerular filtration rate only occurred at a rapid rate after the onset of macroalbuminuria, and that even then, there was a period of 7-10 years until the onset of end-stage renal failure. Thus, there was a window of many years during which patients might have microalbuminuria and a serum creatinine of less than 130-150micromol/l, during which prescription of metformin containing agents such as Avandamet would be appropriate.

A recent sub-analysis of the LIFE study had confirmed the importance of reducing microalbuminuria, suggesting that reduction in urinary albumin excretion after one year of losartan treatment was strongly predictive of mortality, even after adjusting for blood pressure. Evidence from Bakris *et al* (2003) (rosiglitazone monotherapy versus sulphonylurea) and Bakris *et al* (2005) (rosiglitazone and metformin combination versus metformin and sulphonylurea in combination) supported positive effects on both blood pressure and urinary albumin excretion of rosiglitazone as monotherapy or in combination with metformin.

In summary, a large evidence base supported early intervention to reduce blood pressure and urinary albumin excretion in patients with microalbuminuria. Both of these were well validated and accepted parameters of diabetes associated diseases. GlaxoSmithKline believed it was entirely appropriate to refer to secondary effects of Avandamet on urinary albumin excretion as long as these were subsidiary in materials to the primary indication. In addition these effects were only mentioned in the detail aid intended only for secondary care physicians who would find this information relevant and be able to contextualise it in the context of type 2 diabetes. GlaxoSmithKline therefore denied breaches of Clauses 3.2, 7.2 and 7.4.

PANEL RULING

The Panel noted that microalbuminuria was the earliest indicator of nephropathy attributable to diabetes. Left unchecked a patient could progress from having microalbuminuria to eventually having renal failure. The detail aid had previously featured the bold, unqualified headline 'Avandamet delays disease progression'. In that context the Panel considered that the claim 'Help reduce your patients' microalbuminuria' might be taken to imply some degree of renal protection and this was misleading.

The Panel noted that depicted on the page at issue was data showing that rosiglitazone monotherapy reduced the albumin:creatinine ratio by 26.4% at one year (n=57) and that 43% of patients (n=14) had microalbuminuria normalised at one year. There was no data shown for combination therapy with rosiglitazone plus metformin. In this regard the Panel considered that the page which featured the Avandamet product logo was misleading.

Overall the Panel considered that the page was misleading both due to the implication of the renal protection and the use of Avandia data in the context of the Avandamet logo. The claim that Avandamet 'Helps reduce your patients' microalbuminuria' could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled. The Panel did not consider that the claim was inconsistent with the Avandamet SPC. No breach of Clause 3.2 was ruled.

5 Use of inappropriate data to support claims

COMPLAINT

Takeda stated that throughout these pieces Avandia data had been used to support Avandamet claims (eg vascular inflammation, carotid IMT progression rate claims). There were also examples of use of data which used higher doses of the medicines than were recommended in the SPC.

'The maximum recommended daily dose of Avandamet is 8mg rosiglitazone plus 2000mg metformin hydrochloride.'

The risk; benefit of a total daily dose of 8mg rosiglitazone plus 2500mg metformin had therefore not been established.

Furthermore, in accordance with agents in this class, patients commencing treatment with Avandamet needed to undergo careful dose titration, so that the optimal risk:benefit profile was established for each patient, thus Section 4.2 also gave careful dose titration instruction as follows:

'The usual starting dose of Avandamet is 4mg/day rosiglitazone plus 2000mg/day metformin. Rosiglitazone can be increased to 8mg/day after 8 weeks if greater glycaemic control is required.'

There was no mention in these materials of the need for careful titration of Avandamet.

There were several occasions where the data used to support a claim was using a higher dosage of rosiglitazone than the Avandamet presentation (2mg/1000mg) promoted in the pieces.

These were further breaches of Clauses 3.2 and 7.4.

RESPONSE

GlaxoSmithKline stated in relation to the use of rosiglitazone to support claims on Avandamet that:

- The secondary effects on cardiovascular risk factors of rosiglitazone had been established. It was reasonable to assume that when rosiglitazone was given as part of Avandamet that these benefits would be applicable and relevant when bioequivalence of rosiglitazone and metformin given as separate components to Avandamet had been established. The prescribing information of both Avandia and Avandamet was printed on these materials. To preclude the use of such data for a disease such as diabetes was counterintuitive when the licensed and rational use of these medicines was in combination. It would also have significant implications for the use of any data generated with any medicine, when there was a possibility of it being used with any other medicine as part of normal clinical management.
- Studies including Garber *et al* and Stewart *et al* had confirmed no additional glycaemic benefit of metformin doses above 2g and this had been acknowledged in the Avandamet EPAR (as previously discussed).
- Within the context of multiple cardiac risk factor associations with type 2 diabetes, and multiple positive secondary effects of rosiglitazone, it was entirely appropriate to refer to secondary effects of rosiglitazone on cardiovascular risk factors in materials. HDLc and microalbuminuria were only mentioned in secondary care materials.
- In all of GlaxoSmithKline's materials these references were secondary to the primary indication for Avandamet.

PANEL RULING

The Panel noted the very general nature of the complaint and considered that aspects of it had already been ruled upon above.

The Panel was concerned about the vagueness of the complaint and considered that Takeda should be advised that if it wanted to make specific allegations about specific claims then it should make another more detailed complaint.

With regard to the alleged failure to mention the need for careful titration of Avandamet, the Panel noted that the SPC stated that the usual starting dose of Avandamet was 4mg/day rosiglitazone plus 2000mg/day metformin. This could be increased. Dose titration with rosiglitazone (added to the optimal dose of metformin) might be considered before the patient was switched to Avandamet.

In the circumstances the Panel did not consider that the materials were either inconsistent with the SPC or not capable of substantiation and thus ruled no breach of Clauses 3.2 and 7.4 of the Code.

6 Alleged breach of Clause 2 of the Code

COMPLAINT

Takeda stated that, in summary, it was concerned that GlaxoSmithKline had undertaken a major promotional campaign, targeting different health professionals and making a wide range of claims concerning Avandamet's 'beneficial effects' in patients with type 2 diabetes, which were outside the licence, misleading and could not be substantiated. The materials were also unbalanced as undue prominence was given to all these additional benefits and there was very little information concerning the primary indication for Avandamet; namely glycaemic control.

Furthermore in the sales aids one might have expected to have seen data which depicted the safety/tolerability of the product especially as Avandamet was a black triangle product and so the risk:benefit profile of the product was still under intensive review by the Committee on Safety of Medicines.

Such activities could not be in the interest of either the patients or the pharmaceutical industry as a whole and hence Takeda alleged of a breach of Clause 2 of the Code.

RESPONSE

GlaxoSmithKline stated that current NICE guidance on use of glitazones suggested 'effectiveness of glitazone therapy should not only be monitored in terms of glycaemic control, but also by impact on other cardiovascular risk factors …'. Therefore it was relevant to consider the effect of rosiglitazone on a range of cardiovascular risk factors such as blood pressure and microalbuminuria, as long as this was in the context of the primary indication.

In the materials in question, secondary effects were not unduly emphasised, secondary in that they were mediated via insulin resistance as required of GlaxoSmithKline by the MHRA and were in the context of the indication. Therefore GlaxoSmithKline strongly refuted any breach of Clauses 22, 3.2, 7.2 and 7.4 and 2 as alleged.

PANEL RULING

Whilst noting its rulings above the Panel nonetheless did not consider that the matters considered were such as to justify a ruling of a breach of Clause 2 which was reserved as a sign of particular censure.

Complaint received	**27 June 2005**
Case completed	**9 September 2005**

GENERAL PRACTITIONER v DERMAL LABORATORIES

Unsolicited mail

A general practitioner complained that he had received unsolicited mail from Dermal Laboratories, despite on two recent occasions having used the company's own reply paid forms to ask to have his name removed from the mailing lists.

The Panel noted that, according to Dermal's records, the GP had asked on 17 and 24 June to have his practice and home address respectively removed from the company's mailing list. Although Dermal had actioned each request within a week of receipt, a mailing had been assembled and labelled over the three days 21-23 June to be sent out on 24 June. It had thus been impossible to prevent that mailing being dispatched to the complainant.

The Panel noted the course of events and considered that on each occasion Dermal Laboratories had acted quickly to remove the complainant's name and two addresses from its mailing list. It was unfortunate that in the meantime another mailing was being assembled which, due to the lead time, meant that it was sent to the complainant against his wishes. Nonetheless, the Panel considered that Dermal Laboratories had complied promptly with the complainant's requests and so no breach of the Code was ruled.

COMPLAINT

A general practitioner stated that he had received for some time now unsolicited mail from Dermal Laboratories Limited. On two occasions he had used the company's own reply paid forms to ask to have his name removed from the mailing lists but to no avail. Today he received another offer from Dermal Laboratories despite his requests over the last few weeks.

When writing to Dermal Laboratories the Authority asked it to respond in relation to the requirements of Clauses 9.1 and 12.3 of the Code.

RESPONSE

Dermal Laboratories stated that it was always diligent in complying with the Code and it fully endorsed and upheld Clause 9.1. As far as compliance with Clause 12.3 was concerned, the company's records showed that it had received two, separate, written complaints from the complainant – one from his practice address and one from his home address – received on Friday, 17 June, and Friday, 24 June, respectively.

In order to ensure that its correspondence with doctors was correctly addressed and kept up-to-date, Dermal Laboratories employed a reputable mailing agency. On both occasions, having received the complainant's requests, Dermal Laboratories promptly wrote to the agency to instruct it to delete the complainant from the general database for any future mailings from the company. The instructions to the agency were dated 21 June and 28 June and the agency assured the company that its requests were 'actioned' on 24 June and 30 June respectively. In other words, no more than a week elapsed, on either occasion, between the receipt of the requests, their being logged and processed by Dermal Laboratories and it writing to the mailing agency, and the necessary action being implemented by it.

Meanwhile a mailing for Ibugel Forte 10%, booked several weeks previously, was due to leave the agency on Friday, 24 June. This mailing, addressed to a large number of GPs, was being assembled and labelled during the three days prior to 24 June, so as to be sent out on the booked date. From this timetable it would be seen that despite both Dermal Laboratories and its agency acting diligently and promptly, it was impossible to prevent the complainant's 24 June mailing from being despatched. Being sent by second class mail, it might have been delivered a few days later, perhaps adding to the complainant's impression that Dermal Laboratories had been slow off the mark in responding to his request and prompting his complaint.

In the circumstances, given that Dermal Laboratories took no more than a week to arrange for the deletion of the complainant's two addresses from its GP mailing list, held by an outside agency, the company believed it had acted efficiently, correctly and promptly as demanded by Clause 12.3. It was unfortunate that the time interval between when the complainant first wrote and when he received the last mailing might have given him a false impression as explained above.

PANEL RULING

The Panel noted the course of events and considered that on each occasion Dermal Laboratories had acted quickly to remove the complainant's name and two addresses from its mailing list. It was unfortunate that in the meantime another mailing was being assembled which, due to the lead time, meant that it was sent to the complainant against his wishes. Nonetheless, the Panel considered that Dermal Laboratories had complied promptly with the complainant's requests and so no breach of Clause 12.3 was ruled. High standards had been maintained; no breach of Clause 9.1 was ruled.

Complaint received **11 July 2005**

Case completed **10 August 2005**

ANONYMOUS v BRISTOL-MYERS SQUIBB

Taxol support kits

An anonymous complainant alleged that the free supply of support kits by Bristol-Myers Squibb, in association with sales of Taxol (paclitaxel), was an inducement to prescribe.

Taxol concentrate had to be diluted before use and administered intravenously using non-PVC equipment. The support kits contained normal saline infusion in a non-PVC bag, a non-PVC giving set with integral filter and an instruction leaflet.

The Panel considered that the free supply of the support kits with the purchase of Taxol constituted a package deal. The supplementary information to the Code stated that the Code did not prevent the offer of such deals whereby the purchaser of a particular medicine received with them other associated benefits, such as apparatus for administration, provided that the transaction as a whole was fair and reasonable and the associated benefits were relevant to the medicines involved. The Panel considered that the support kit was relevant to the supply of Taxol and that the transaction was fair and reasonable. No breach of the Code was ruled.

An anonymous complainant complained about the free supply of support kits by Bristol-Myers Squibb in association with sales of Taxol (paclitaxel). Taxol was an intravenous chemotherapeutic agent to be administered through an in-line filter with a microporous membrane ≤ 0.22 micron. The product was presented as a concentrate to be diluted before use in, *inter alia*, normal saline. The summary of product characteristics (SPC) specifically stated that equipment used in the preparation, storage and administration of Taxol had to be non-PVC. The support kits contained 500ml normal saline infusion in a non-PVC bag, a non-PVC giving set with an integral 0.22 micron filter and an instruction leaflet.

COMPLAINT

The complainant alleged that the supply of the free support kits with sales of Taxol was an inducement to prescribe.

Bristol-Myers Squibb was asked to respond in relation to the requirements of Clause 18.1 of the Code.

RESPONSE

Bristol-Myers Squibb explained that free support kits with Taxol had been used since early clinical trials were conducted prior to the UK product launch in 1993. The vehicle in the Taxol solution leached plasticisers from PVC and so to avoid potential safety issues which might arise if patients were exposed to these agents Bristol-Myers Squibb had always recommended that Taxol be administered in non-PVC equipment. When trials began in the UK over 12 years ago, non-PVC giving sets etc were difficult to source and so for convenience and safety Bristol-Myers Squibb sourced and supplied the non-PVC constituents of the support kits.

When Taxol was launched in the UK it was still difficult to source non-PVC equipment so Bristol-Myers Squibb continued to provide these kits, free of charge, with Taxol to customers that required them. As there were no alternative products available on the market, the support kits could not be seen as an inducement to prescribe Taxol at that time.

Although non-PVC infusion bags, giving sets and filters were now more readily available the suitability of these depended on the compatibility of individual components with particular infusion pumps. A survey to determine whether there was still a need to provide support kits indicated that some hospitals still required them. Bristol-Myers Squibb's supply of Taxol support kits provided peace of mind that patients had appropriate administration devices for the product.

Bristol-Myers Squibb stated that support kits were available, at no charge, as a value added service to the NHS, to any purchaser of the product that required them and also with clinical trial stock for investigator-led studies. Kits were not given to purchasers who did not require them. Each kit cost Bristol-Myers Squibb a fraction of the total purchase price of Taxol (approximate price of one cycle of Taxol treatment was currently £1043), so it was difficult to see how this service constituted an inducement to prescribe. Additionally, Bristol-Myers Squibb understood that new paclitaxel suppliers were now offering this service. Recently, companies were asked to tender, on a national basis, for supply of paclitaxel and in recognition of the utility of providing support kits to the NHS, they were asked if they would supply such kits with their product. In the tender document placed by Bristol-Myers Squibb, the company agreed to continue providing support kits. Other customers had also been informed of this intention when involved in purchasing discussions with Bristol-Myers Squibb.

Bristol-Myers Squibb referred to the supplementary information to Clause 18 of the Code and submitted that the support kits were medical goods which enhanced patient care and benefited the NHS. Provision of the kits was not an inducement to prescribe; representatives were not involved with their distribution and so there was no link between the promotion of Taxol and the provision of the kits; the remuneration for Bristol-Myers Squibb's distributors was not linked to sales of Taxol and the instructions leaflet was for health professionals only and its content was non-promotional.

Bristol-Myers Squibb submitted that it provided appropriate information to purchasers about the provision of the Taxol support kits in that it complied with that part of the supplementary information to Clause 18.1 of the Code, which stated: 'Companies are recommended to inform relevant parties, such as NHS

trusts, health authorities, health boards and primary care organisations of their activities where appropriate. This is particularly recommended where companies are proposing to provide goods and services which have budgetary implications for parties involved'.

Bristol-Myers Squibb stated that the kits did not offer any personal benefit to the health professional and, therefore, could not be considered an inducement to prescribe.

Bristol-Myers Squibb further noted that the supplementary information to Clause 18.1, Package Deals, stated that Clause 18.1 did not prevent the offer of package deals whereby the purchaser of a particular medicine received with them other associated benefits such as apparatus for administration, providing that the transaction as a whole was fair, reasonable, and the associated benefits were relevant to the medicine involved. The company submitted that provision of the support kits was a 'package deal' and consequently was justified under the Code.

Bristol-Myers Squibb considered that the provision of support kits should not be subject to the Code by virtue of the discounting exemption stated in Clause 1.2. The kits were part of the commercial arrangements and overall value proposition for Taxol in terms of the medicine and patient care issues. This type of value-added arrangement was a discount for the purposes of UK competition law and was a strategy commonly used by the pharmaceutical industry on 1 January 1993, so that the exemption in Clause 1.2 applied.

In conclusion, Bristol-Myers Squibb strongly refuted that supply of support kits with Taxol constituted an inducement to prescribe or was any way contrary to the Code. On the contrary this type of service would be permitted by the Code because: use of the kits was consistent with the administration requirements detailed in the Taxol SPC; support kits were provided as a service to the NHS to enhance patient care and did not offer any personal benefit to a health professional; information provided to potential purchasers complied with the recommendation that relevant parties should be informed of activities that might have budgetary implications, Bristol-Myers Squibb employees were not directly involved in the distribution of support kits and representatives did not distribute written promotional material concerning the support kits; provision of support kits was initiated in 1993 due to safety concerns over use of the more readily available PVC kits and the difficulty in obtaining the recommended non-PVC equipment and continuation of the supply was evaluated more recently and considered important for patient safety.

PANEL RULING

The Panel considered that the free supply of the support kits with the purchase of Taxol constituted a package deal. The supplementary information to Clause 18.1 of the Code, Package Deals, stated that Clause 18.1 did not prevent the offer of such deals whereby the purchaser of a particular medicine received with them other associated benefits, such as apparatus for administration, provided that the transaction as a whole was fair and reasonable and the associated benefits were relevant to the medicines involved. The Panel considered that the support kit was relevant to the supply of Taxol and that the transaction was fair and reasonable. No breach of Clause 18.1 was ruled.

Complaint received **12 July 2005**

Case completed **28 July 2005**

CASE AUTH/1735/7/05

NOVO NORDISK v SANOFI-AVENTIS

Letter to health professionals

Novo Nordisk complained about a letter sent to diabetologists, diabetic specialist nurses and general practitioners by Sanofi-Aventis detailing the company's insulin portfolio. Novo Nordisk alleged that the opening statement of the letter 'announcements from another insulin manufacturer, Novo Nordisk, regarding the proposed discontinuation of several presentations of major insulin brands, has caused some confusion and in some cases disappointment' disparaged the activities of a fellow pharmaceutical company and risked bringing disrepute to the pharmaceutical industry. Novo Nordisk further noted that although the letter referred to products such as Insuman, Lantus and Apidra, and was thus promotional, there was no prescribing information and nor did the non-proprietary names appear immediately adjacent to the brand names.

Novo Nordisk also alleged that the claim that the OptiClik pen 'represents a big step forward in insulin delivery and has several unique benefits over existing delivery devices' was not substantiated and misleading. The statement 'over existing delivery devices' was an ambiguous hanging comparison as the comparator(s) was not named.

The Panel considered that the effect of the letter was, *inter alia*, to favourably highlight the availability of Sanofi-Aventis' insulin portfolio within the context of critical comment on the discontinuation of several presentations of major insulin brands by Novo Nordisk. Information about the forthcoming OptiClik device and Apidra was given. Claims were made that the OptiClik pen represented 'a big step forward in insulin delivery' and that Apidra was a 'rapid acting insulin analogue'. The Panel considered that the letter was thus subject to the Code.

The Panel noted that discontinuation of products might give rise to concern and disappointment, nonetheless it was a legitimate business activity. The Panel noted that letters showed that one clinician was concerned regarding Novo Nordisk's plans to withdraw some of its insulins; it did not appear, however, that he was confused with regards to Novo Nordisk's plans. Information issued by a diabetes charity also showed that the organisation, although unhappy about Novo Nordisk's decision, was not confused about it. The letter from Sanofi-Aventis stated that Novo Nordisk's announcements had caused confusion but there was no evidence that that was so. In that regard the statement at issue was disparaging and misleading as alleged; breaches of the Code were ruled. With regard to the statement that Novo Nordisk's plans had caused disappointment the Panel noted that critical comments about either a company or its products were acceptable under the Code provided that they were accurate, balanced, fair etc and could be substantiated, Novo Nordisk's decision to withdraw some of its products had clearly disappointed some customers and organisations. No breach of the Code was ruled.

The Panel considered that the letter required prescribing information for all of the insulins mentioned. In addition the non-proprietary name needed to be immediately adjacent to the most prominent display of each brand name. No prescribing information was provided. A breach of the Code was ruled. The non-proprietary name for Apidra appeared immediately adjacent to the brand name and no breach was thus ruled in this regard. However, such information was absent for the other products and a breach of the Code was ruled.

The Panel noted Sanofi-Aventis' submission that the OptiClik pen was a delivery device for Lantus. In the Panel's view promotion of the device was, therefore, in effect, promotion of Lantus. Sanofi-Aventis had not provided any data to substantiate the claim that the pen 'represents a big step forward in insulin delivery and has several unique benefits over existing delivery devices' thus a breach of the Code was ruled. A further breach was ruled in that the Panel considered that the claim 'several unique benefits' was ill defined and thus misleading. The Panel did not consider that the phrase 'over existing delivery devices' was a hanging comparison as alleged. The comparator was existing delivery devices. No breach of the Code was ruled on this point.

Novo Nordisk Limited complained about a letter sent to diabetologists, diabetic specialist nurses and general practitioners (GPs) with a special interest in diabetes by Sanofi-Aventis in June 2005 detailing the company's insulin portfolio. The letter began by referring to the proposed discontinuation of major insulin brands by Novo Nordisk.

COMPLAINT

Novo Nordisk alleged that the opening statement of the letter 'announcements from another insulin manufacturer, Novo Nordisk, regarding the proposed discontinuation of several presentations of major insulin brands, has caused some confusion and in some cases disappointment' disparaged the activities of a fellow pharmaceutical company with unsubstantiated comments such as 'confusion' and 'disappointment' in breach of Clauses 8.1 and 7.2. Such direct negative reference to another pharmaceutical company risked bringing disrepute to the pharmaceutical industry and Sanofi-Aventis had done the industry a disservice.

Novo Nordisk further noted that although the letter carried a long list of branded products such as Insuman and Lantus, and was thus promotional, there was no prescribing information and nor did the non-proprietary names appear immediately adjacent to the brand names. Breaches of Clauses 4.1 and 4.3 were alleged.

Thirdly, Novo Nordisk alleged that the claim that the OptiClik pen 'represents a big step forward in insulin delivery and has several unique benefits over existing delivery devices' was not substantiated by any data in breach of Clause 7.4. The statement 'several unique benefits' was misleading and the statement 'over

existing delivery devices' was an ambiguous hanging comparison as the comparator(s) were not named. A breach of Clause 7.2 was alleged.

Finally, Novo Nordisk noted that a bullet point referred to Apidra (insulin glulisine). Again no prescribing information for Apidra was attached, in breach of Clause 4.1. The non-proprietary name was not adjacent to the brand name Apidra in breach of Clause 4.3.

RESPONSE

Sanofi-Aventis queried whether the letter was promotional: it was designed to be a 'factual, accurate and informative announcement', as described in Clause 1.2 of the Code, relating to the company's assurance of supply of medicines as well as a variation of an additional pen system for Lantus. The letter did not include claims for any of the medicines and Sanofi-Aventis considered a claim for a medical device to be outside the scope of the Code.

Sanofi-Aventis considered the statements in the letter about Novo Nordisk were factual and substantiable. A highly regarded UK charity, had stated that it was unhappy about the withdrawal of Actrapid [Novo Nordisk's product]. Sanofi-Aventis provided confidential copies of letters from clinicians as further substantiation.

Sanofi-Aventis stated that the letter was issued in response to concerns already highlighted. As there were no additional product claims, the company did not consider that the letter was a promotional item under Clause 1.1 which excluded the need for prescribing information.

Sanofi-Aventis stated that the sentence regarding the OptiClik pen referred to the aspect of insulin delivery, rather than a claim about any benefits of Lantus, itself. Therefore, the company also considered that this did not constitute a promotional claim about a medicine as defined by Clause 1.1 and therefore did not consider that the Code applied. Sanofi-Aventis noted that other insulin devices (reusable part) were not classified as prescription only medicines.

Sanofi-Aventis noted that Clause 4.3 stated that a black triangle was required on promotional material. As the company did not consider the letter was a promotional item, it did not consider that the black triangle was required. The non-proprietary name for Apidra, insulin glulisine, was clearly placed adjacent to the first instance of 'Apidra'. The reason that the non-proprietary name for Apidra was given but that for other insulins referred to was not, was because although the medicine had been approved by the European Medicine Evaluation Agency clinicians might not be familiar with it as it had not yet been marketed.

PANEL RULING

The Panel noted that the first paragraph of the letter referred to the discontinuation of several presentations of major insulin brands by Novo Nordisk and stated that this had caused 'some confusion and in some cases disappointment'. The second paragraph explained that the purpose of the letter was to reassure and clarify the position regarding the availability of the Sanofi-Aventis portfolio; a list of insulins marketed by Sanofi-Aventis followed. Reference was made to newer insulins which were supported by good clinical evidence. Two bullet points each introduced the company's new products; the OptiClik pen delivery device for Lantus and Apidra, an insulin analogue which the company hoped would be available in early 2006.

Firstly, the Panel had to decide whether the letter was subject to the Code. The Panel did not consider that the letter could take the benefit of the exemption to the definition of promotion set out in Clause 1.2 which related to factual, accurate informative announcements and reference material concerning licensed medicines relating for example to pack changes, adverse reaction warnings, trade catalogues and price lists, provided they included no product claims. The Panel considered that the effect of the letter was, *inter alia*, to favourably highlight the availability of Sanofi-Aventis' insulin portfolio within the context of critical comment on the discontinuation of several presentations of major insulin brands by Novo Nordisk. Information about the forthcoming OptiClik device and Apidra was given. Claims were made that the OptiClik pen represented 'a big step forward in insulin delivery' and that Apidra was a 'rapid acting insulin analogue'. The Panel considered that the letter met the definition of promotion set out in Clause 1.2 of the Code; it would promote the prescription, supply, sale or administration of Sanofi-Aventis' medicines. It was thus subject to the Code.

The Panel noted that discontinuation of products might give rise to concern and disappointment, nonetheless it was a legitimate business activity. The Panel noted that copies of two letters from a single clinician were provided which clearly showed that he was concerned regarding Novo Nordisk's plans to withdraw some of its insulins; it did not appear, however, that he was confused with regards to Novo Nordisk's plans. Information issued by a diabetes charity also showed that the organisation, although unhappy about Novo Nordisk's decision, was not confused about it. The letter from Sanofi-Aventis stated that Novo Nordisk's announcements had caused confusion but there was no evidence that that was so. In that regard the statement at issue was disparaging and misleading as alleged; breaches of Clauses 7.2 and 8.1 were ruled. With regard to the statement that Novo Nordisk's plans had caused disappointment the Panel noted that critical comments about either a company or its products were acceptable under the Code provided that they were accurate, balanced, fair etc and could be substantiated, Novo Nordisk's decision to withdraw some of its products had clearly disappointed some customers and organisations. No breach of Clauses 7.2 and 8.1 was ruled.

The Panel considered that the letter required prescribing information for all of the insulins mentioned. In addition the non-proprietary name of each insulin needed to be stated immediately adjacent to the most prominent display of each brand name. There was no prescribing information provided for

any of the insulins referred to. A breach of Clause 4.1 was ruled. Further, only the non-proprietary name of Apidra was stated immediately adjacent to the brand name; such information was absent for the other brands and a breach of Clause 4.3 was ruled. No breach of Clause 4.3 was ruled with regard to Apidra.

The Panel noted Sanofi-Aventis' submission that the OptiClik pen was a delivery device for Lantus. In the Panel's view promotion of the device was, therefore, in effect, promotion of Lantus. The Panel thus considered that the promotion of the device was subject to the Code. The Panel noted that Sanofi-Aventis had not provided any data to substantiate the claim that the OptiClik pen 'represents a big step forward in insulin delivery and has several unique benefits over existing delivery devices'. A breach of Clause 7.4 was ruled.

The Panel noted that Novo Nordisk had not explained why it considered the phrase 'several unique benefits' to be misleading. The Panel noted that the supplementary information to Clause 7.10, Use of the Words 'The' and 'Unique', explained that great care needed to be taken with the use of the word 'unique'. Although it might be used to describe some clearly defined special feature of a medicine, in many instances it might simply imply a general superiority. In such instances it was not possible to substantiate the claim as the claim itself was so ill defined. The Panel considered that the claim 'several unique benefits' was ill defined and so was misleading in that regard. A breach of Clause 7.2 was ruled.

The Panel did not consider that the phrase 'over existing delivery devices' was a hanging comparison as alleged. The comparator was existing delivery devices. No breach of Clause 7.2 was ruled on this point.

Complaint received **13 July 2005**

Case completed **20 September 2005**

CASE AUTH/1736/7/05

ROCHE v ABBOTT

Reductil leavepiece

Roche complained about a Reductil (sibutramine) leavepiece issued by Abbott. Reductil was an adjunctive therapy within a weight management programme for patients with either a body mass index (BMI) of ≥ 30kg/m^2 or ≥ 27kg/m^2 if other obesity related risk factors such as type 2 diabetes or dyslipidaemia were present. Roche supplied Xenical (orlistat) which was a similarly indicated adjunctive therapy for weight loss.

Roche noted that the claim 'Reductil is more effective than orlistat' appeared on page 5 of the leavepiece and was referenced to Sari *et al* (2004), a small-scale, open-label, six month study conducted in Turkey, which directly compared sibutramine and orlistat. The study population was 89 housewives with a BMI ≥ 30kg/m^2 and no significant co-morbidity. No men were included. The population sample was not representative of the wider UK obese population and this data did not represent the balance of evidence.

Xenical and Reductil had different mechanisms of action. Xenical was a gastrointestinal lipase inhibitor which decreased fat absorption by binding to pancreatic lipase and increasing faecal fat excretion. Reductil, however, was a centrally-acting serotonin and norepinephrine reuptake inhibitor. Any head-to-head study therefore that did not ensure adequate dietary compliance and monitoring was likely to be inherently biased towards the medicine whose posology and method of administration did not include dietary instructions.

Roche stated that the percentage of non-responders (<5% weight loss) in the Xenical arm of Sari *et al* was high compared with larger, double-blind, placebo controlled trials with Xenical in 12 month studies (Torgerson *et al* 2004, Davidson *et al* 1999, Sjostrom *et al* 1998 and Rissanen *et al* 2003). One would expect 12 month non-responder figures to be higher, as they would include all those losing <5% weight at 6 months and beyond. In the study 44% failed to respond; however, the balance of evidence from 12 month studies, showed that non-responders made up only approximately 30%. This anomaly suggested that the standards of dietary instruction and compliance monitoring in the study were not similar to other studies. The Xenical summary of product characteristics (SPC) recommended that Xenical was taken in conjunction with a mildly hypocaloric diet that contained approximately 30% of calories from fat.

Furthermore, the claim followed two full pages highlighting the positive effects of Reductil on HbA_{1c} and lipids and thus implied that Reductil was more effective than Xenical in reducing these risk factors and weight loss.

Roche alleged that the claim was all-embracing, unsupported by Sari *et al*, and misleading.

Roche noted that in intercompany correspondence Abbott had referred to a number of papers as supporting its claim. Roche alleged that these papers did not provide an up-to-date evaluation of all the evidence available.

The Panel noted that it had been provided with four meta-analyses regarding the pharmacological management of weight reduction (Haddock *et al*, Padwal *et al*, Avenell *et al* and Norris *et al*). All of these studies reported a greater weight loss with Reductil than with Xenical. The weight loss at one

year with Xenical was 2-3.01kg and for Reductil was 3.5-5.1kg. None of the meta-analyses drew any conclusions with regard to the statistical significance of these differences; Padwal *et al* and Norris *et al* noted that the magnitude of weight loss seen with both therapies was modest. Avenell *et al* stated that although trials of Xenical showed slightly less weight loss than with Reductil, Xenical had a more beneficial effect on risk factors. Haddock *et al* noted that 'no drug, or class of drugs, demonstrated clear superiority as an obesity medication'.

The claim at issue 'Reductil is more effective than [Xenical]' was referenced to Sari *et al*. This was a short-term study and involved small numbers of patients. Weight loss at 6 months was 5.5kg (5.5%) in the Xenical group (n=30) and 10.1kg (10.2%) in the Reductil group (n=29). Although the relative efficacy of the two medicines mirrored that seen in the meta-analyses, the magnitude of the weight loss was about double that which might normally be expected.

The Panel noted that other direct comparative studies had been cited by the parties. Derosa *et al* (2005) and Derosa *et al* (2004) both failed to show any statistically significant difference between Xenical and Reductil in terms of weight loss. The Panel noted, however, that the dose of Reductil in both studies was 10mg/day and not the maximum permitted dose of 15mg/day. Kaya *et al* was another short-term study with small groups of patients which, like Sari *et al*, reported weight loss in excess of what might normally be expected (Xenical 360mg/day, n=25, –9.35kg; Reductil 10mg/day, n=22, –11.72kg, p=0.02).

The Panel noted that the meta-analyses had not reported a statistically significant difference in terms of weight loss between the two therapies. The two direct comparisons which had reported a statistically significant difference (Sari *et al* and Kaya *et al*) were short term and the absolute weight losses reported for Xenical and Reductil in each were atypical. On balance, the Panel did not consider that it had been unequivocally proven that Reductil caused more weight loss than Xenical such that the difference between the two was statistically significant as implied by the claim. Breaches of the Code were ruled.

The Panel considered that the claim 'Reductil is more effective than [Xenical]' was a broad, unqualified claim; it was unclear as to what aspect of therapy it referred. Preceding pages had detailed the effect of Reductil on HbA_{1c} and lipids. Given the unqualified nature of the claim the Panel considered that it was all embracing as alleged. A breach of the Code was ruled.

Roche noted the claim '86% of diabetic patients treated with Reductil 15mg demonstrated a concomitant fall in HbA_{1c} of >1%' was referenced to McNulty *et al* (2003). Roche alleged that notwithstanding the page heading 'Weight loss with Reductil has a positive effect on HbA_{1c}', which clearly suggested that the improvement in glycaemic control was related to weight loss, the bullet point inferred that Reductil improved HbA_{1c} in the majority of diabetic patients. This was misleading, particularly given evidence from clinical guidelines for type 2 diabetes published in 2001 by the Royal College of General Practitioners, The Royal College of Physicians and the Royal College of Nursing, which recommended only Xenical as a suitable anti-obesity medicine in the management of type 2 diabetes. This evidence was also reflected in the National Institute of Clinical Excellence (NICE) guideline on the management of blood glucose.

Roche alleged that the footnote, 'Please note Reductil is not licensed for treatment of type 2 diabetes' suggested that it was recognized that this statement could lead to inappropriate use of Reductil to treat diabetic patients. The Reductil SPC suggested that weight loss with Reductil 'was associated with a mean reduction of 0.6% in HbA_{1c}'.

Roche alleged that in summary, the claim regarding the benefits of Reductil in the treatment of type 2 diabetics was not in accord with the SPC and was not supported by the established, independent NICE guidelines on the use of anti-obesity medicines in the management of type 2 diabetes and was therefore in breach of the Code.

The Panel noted that although clinical guidelines recommended the use of Xenical as part of a weight loss strategy in type 2 diabetics, they did not state that Reductil should not be used. Reductil was not contra-indicated in type 2 diabetes nor were there any special warnings or special precautions for use in such a patient population. Section 5.1 of the Reductil SPC, Pharmacodynamic properties, stated 'In obese patients with type 2 diabetes mellitus weight loss with [Reductil] was associated with mean reductions of 0.6% (unit) in HbA_{1c}'. The claim at issue '86% of diabetic patients treated with Reductil 15mg demonstrated a concomitant fall in HbA1c of >1%', however, suggested a greater reduction would be seen in most patients. The Panel considered that the claim was thus inconsistent with the particulars listed in the Reductil SPC. A breach of the Code was ruled.

Roche Products Limited complained about the promotion of Reductil (sibutramine) by Abbott Laboratories Limited. The item at issue was a six page, gate-folded leavepiece (ref PXRED20050085). Reductil was an adjunctive therapy within a weight management programme for patients with either a body mass index (BMI) of $\geq 30kg/m^2$ or $\geq 27kg/m^2$ if other obesity related risk factors such as type 2 diabetes or dyslipidaemia were present.

Roche supplied Xenical (orlistat) which was a similarly indicated adjunctive therapy for weight loss.

Intercompany correspondence failed to resolve the issues.

1 Claim 'Reductil is more effective than orlistat'

The claim appeared on page 5 of the leavepiece and was referenced to Sari *et al* (2004), a direct comparison of sibutramine and orlistat.

COMPLAINT

Roche noted that Sari *et al* was a small-scale, open-label, six month study conducted in Turkey. The

study population was 89 housewives with a BMI ≥ 30kg/m^2 and no significant co-morbidity, such as diabetes, hypertension or serious cardiovascular disease, conditions that commonly co-existed in obesity. No men were included. The population sample was not representative of the wider UK obese population and the results could not be extrapolated and generalized as inferred. Furthermore, this data did not represent the balance of evidence.

Xenical and Reductil had different mechanisms of action. Xenical was a gastrointestinal lipase inhibitor which decreased fat absorption by binding to pancreatic lipase and increasing faecal fat excretion. Reductil, however, was a centrally-acting serotonin and norepinephrine reuptake inhibitor. Any head-to-head study therefore that did not ensure adequate dietary compliance and monitoring was likely to be inherently biased, towards the medicine whose posology and method of administration did not include dietary instructions.

The percentage of non-responders (<5% weight loss) in the Xenical arm of Sari *et al* was high compared with larger, double-blind, placebo controlled trials with Xenical for which data at 12 months was available (Torgerson *et al* 2004, Davidson *et al* 1999, Sjostrom *et al* 1998 and Rissanen *et al* 2003). However, Roche alleged that one would expect 12 month non-responder figures to be higher, as they would include all those losing <5% weight at 6 months and beyond. In the study 44% failed to respond; however, the balance of evidence from 12 month studies, showed that non-responders made up only approximately 30%. This anomaly suggested that the level of dietary instructions given and compliance monitoring in the study could not have been of a similar standard to that in other studies. The Xenical summary of product characteristics (SPC) recommended that Xenical was taken in conjunction with a mildly hypocaloric diet that contained approximately 30% of calories from fat.

Furthermore, the claim followed two full pages highlighting the positive effects of Reductil on HbA_{1c} and lipids and thus implied that Reductil was more effective than Xenical in reducing these risk factors and weight loss.

Roche alleged that the claim was all-embracing, unsupported by Sari *et al*, and misleading in breach of Clauses 7.2, 7.3 and 7.10.

Roche noted that in intercompany correspondence Abbott had referred to the following papers as 'supporting' its claim. Roche alleged that these papers did not provide an up-to-date evaluation of all the evidence available.

Kaya *et al* (2004) looked at changes in anthropometric measures of obese patients treated with diet and exercise alone, or in addition to Reductil 10mg daily, Xenical 120mg tds or both medicines combined. This open-label, short-term study (12 weeks) involved only 86 Turkish patients and excluded those with uncontrolled hypertension and a history of diabetes. Differences between Turkish and UK dietary lifestyle again made the results difficult to extrapolate to the UK. Therefore this study could not support the claim of superior efficacy in weight loss or reduction in co-morbidities.

The 2005 Cochrane review (Norris *et al* 2005) was a meta-analysis of four Xenical and four Reductil studies. Study duration was 52-57 weeks with Xenical and only 12-26 weeks with Reductil. It was known from clinical trials involving a variety of weight loss mechanisms that the rate of weight loss was highest in the first few months of treatment and then decreased over time.

Furthermore, one of the Reductil studies (Gokcel *et al* 2001) in the meta-analysis, used twice the recommended, and unlicensed, dose of 10mg bd. If this study was excluded from the meta-analysis, then the pooled effect showed a reduction of 2.5kg with Reductil compared to 2.6kg with Xenical, notwithstanding the different duration of therapies. Only Xenical was associated with statistically significant improvements in total cholesterol, LDL and triglyceride sustained at 52 weeks. Therefore the large discrepancies in duration of study treatment and the unlicensed dose of Reductil used in one study, meant that the results of this meta-analysis could not support the claim of superior efficacy in weight loss or reduction in co-morbidities.

The 2003 Cochrane meta-analysis (Padwal *et al* 2003) included eleven Xenical and three Reductil studies. This included Xenical studies, but no Reductil studies, with obese diabetic patients where weight management was known to be more difficult compared to the obese non-diabetic population. In addition the co-intervention in the Reductil studies consisted of simple 'dietary advice sheets' whereas the Xenical studies included dietary counselling, food intake diary, 600-900kcal/day deficit diet in line with the SPC, and exercise. The more intensive behavioural regime in the Xenical studies was reflected in the higher weight loss achieved in the Xenical placebo arm compared with the Reductil placebo arm. The figures quoted by Abbott as 'demonstrating Reductil to be more effective pharmacotherapy for weight loss' in fact compared the treatment arms to their own individual placebo arms and was not a direct comparison. In addition, Reductil caused significant increase in diastolic and systolic blood pressure and pulse and had no significant beneficial effect on lipids and glycaemic control. Therefore this meta-analysis could not support the claim of superior efficacy in weight loss or reduction in co-morbidities.

Roche noted that neither of the two Cochrane meta-analyses (Norris *et al*, Padwal *et al*) concluded that Xenical or Reductil were superior in terms of weight loss.

A third meta-analysis, Haddock *et al* (2002), referred to by Abbott concluded that 'no drug, or class of drugs, demonstrated clear superiority as obesity medication'. The effect size 95% confidence interval that was referred to by Abbott represented post-test outcomes of studies without consideration of design differences, such as study length, dose, etc. The mean number of weeks of treatment with Xenical was 47.5 weeks compared with 14.5 weeks with Reductil. The importance of duration of therapy had already been addressed. In addition the placebo group in the Xenical studies lost a mean of 5.02kg compared with 1.8kg in the Reductil studies. This meta-analysis

therefore could not support the superiority claim in weight loss or reduction of co-morbidities.

In addition, there was a number of studies not previously referred to that provided evidence that clearly did not support the claim or provided evidence to suggest the contrary.

Research findings from the recent NHS Research and Development Health Technology Assessment (HTA) Programme (Avenell *et al* 2004) provided the most comprehensive, independent systematic review of obesity treatments in adults to date. The methods of the Cochrane Collaboration were applied and randomized controlled trials, with a follow-up of at least one year, were evaluated. The results demonstrated that Xenical and Reductil were associated with similar weight changes at 12 months, –3.01kg (95% CI –3.48 to –2.54kg) for Xenical and –4.12kg (95% CI –4.9kg to –3kg) for Reductil. These weight changes were little changed at later time points, –3.26kg (95% CI –4.15 to –2.37kg) at 24 months for Xenical and –3.4kg (95% CI –4.45kg to –2.35kg) at 18 months for Reductil. There was no significant difference in weight loss between the two groups.

The review found that Xenical and Reductil had different effects on lipids and blood pressure. Weight reduction with Reductil was associated with a significant beneficial effect on HDL cholesterol and triglycerides at 12 months, but not on any other risk factors. However in the Xenical studies, there were significant beneficial effects in total cholesterol, LDL cholesterol and HDL cholesterol. In addition, the review found that in the Reductil groups there was an increase in systolic blood pressure and a significant increase in diastolic blood pressure observed at 12 months. In the Xenical studies there was a significant reduction in both diastolic and systolic blood pressure. The authors concluded that 'the apparent beneficial effects of sibutramine on weight and risk factors need to be balanced against the potential increase in blood pressure'.

Derosa *et al* (2004) evaluated the efficacy and safety of Xenical and Reductil in a 12 month, double-blind, randomized, controlled study in obese diabetics (n=144). The authors concluded that Xenical was more efficacious as an anti-obesity medicine compared with Reductil; in addition a significant improvement in blood pressure was only evident in the Xenical group.

Derosa *et al* (2005) evaluated the efficacy and safety of Xenical and Reductil in obese hypertensives (n=115). Patients in this controlled, double-blind, 12 month study were randomized to either Xenical 120mg tds or Reductil 10mg. Significant reductions in BMI were evident after 6, 9 and 12 months and were similar in both groups (at 6 months –1.9 Xenical v –1.8 Reductil, at 9 months –2.3 v –2.2, at 12 months –2.9 v –2.8). At the end of the study, patients obtained a similar weight reduction of 8.9% in the Xenical group and 8.6% in the Reductil group. Only patients in the Xenical group, however, experienced significant improvements in blood pressure, total cholesterol and LDL cholesterol after 12 months (Norris *et al*). In summary, the overarching claim that Reductil was more effective than Xenical was not substantiated by the data and made no allowance for the differences in lipid response, blood pressure and heart rate.

Roche alleged that the claim 'Reductil is more effective than orlistat' did not reflect the full balance of evidence and therefore could not be substantiated, in breach of Clause 7.4.

In addition the claim did not take into account the restrictions in the use of Reductil that were not shared by Xenical such as patients with a history of depression, epilepsy, mild to moderate hepatic impairment, mild to moderate renal impairment, history of major eating disorders, open angle glaucoma, patients who were at risk of raised intraocular pressure, patients predisposed to bleeding events and patients with a family history of motor or verbal tics. Moreover the cited study (Sari *et al*) was inappropriate as the patients did not reflect the population of the UK and there was no recognition of the posology of the Xenical SPC.

RESPONSE

Abbott stated that it was not aware of a single published head-to-head trial that had conclusively demonstrated the equivalence or non-inferiority of Xenical and Reductil. Nor had a head-to-head trial ever demonstrated that Xenical produced greater weight loss than Reductil. Roche had also been unable to provide evidence of a study of this nature. Sari *et al*, however, cited in the leavepiece demonstrated that Reductil produced a statistically significant greater weight loss than Xenical.

Abbott noted that in intercompany correspondence Roche had referred to two studies, Derosa *et al* (2004) and Derosa *et al* (2005), which were designed to demonstrate superiority, but which were unable to do so, as evidence of equivalent efficacy for the two interventions. This was obviously not the case; if a clinical trial failed to demonstrate superiority one could not assume equivalence – absence of evidence was not evidence of absence. The reason that these two studies failed to demonstrate the superior weight loss demonstrated with Reductil in other head-to-head trials was mainly due to use of an inadequate dose. Roche had not addressed these issues, focussing instead on a discussion around secondary endpoints and concomitant effects on co-morbidities.

Abbott noted Roche's comments relating to this evidence base and claims that the head-to-head studies were 'inherently biased' towards Reductil because the 'posology and method of instruction did not include dietary instructions'. The SPC for Reductil clearly stated that Reductil should only be prescribed in the context of dietary modification. Furthermore in all of the head-to-head studies all patients were given identical dietary advice thus eliminating any potential for diet-related bias. Any such bias, if it did exist, would also infer that the weight loss due to Xenical should be mainly attributed to the accompanying dietary intervention. Abbott submitted that if anything this added credence to its claim that Reductil was more effective than Xenical.

Abbott submitted that any potential bias relating to diet that might exist would be insignificant when

compared to the bias associated with comparing results from separate studies, whether comparing weight loss alone or proportions of responder vs non-responders. Again, such an approach was not consistent with the application of evidence-based medicine and rendered the citations by Roche (Torgerson *et al*, Davidson *et al*, Sjostrom *et al* and Rissanen *et al*) detailing the efficacy of Xenical vs placebo, irrelevant to the issue at hand.

Abbott submitted that it could provide many examples of Reductil studies where weight loss was greater than that demonstrated in the head-to-head studies but the only way to compare medicines by analysing data from a number of different studies was through meta-analysis. This was covered in more detail below.

Abbott stated that it cited a single head-to-head trial on the item in question as a comparison was always the most straightforward way to compare two interventions. Roche had criticised this study based on the inclusion and exclusion criteria and possible regional differences in diet (a criticism hard to understand as both arms of the study would have lived in the same country). It was, however, reasonable to ask for substantiation of such a claim that went beyond a single clinical trial. Abbott submitted that this was why during intercompany correspondence it had cited another head-to-head study (Kaya *et al*) and three independent meta-analyses (Norris *et al*, Padwal *et al* and Haddock *et al*) as further substantiation. Abbott, therefore, denied a breach of Clause 7.4.

Abbott stated that Roche's critique of the Cochrane meta-analyses did not take away from the fact that these were independently produced, robust and thorough reviews which combined data from numerous clinical trials. Cochrane meta-analyses were particularly well respected and entirely independent in nature. Both meta-analyses clearly demonstrated that Reductil produced statistically significantly greater weight loss than Xenical when used to treat obese patients either with or without diabetes.

Abbott submitted that the 2005 Cochrane review (Norris *et al*) established a mean weight loss of 2kg for Xenical (95% CI, 1.3kg-2.8kg) whereas for Reductil the mean weight loss was 5.1kg (95% 3.2kg-7.0kg). This was a conclusive result. Reductil clearly produced a greater weight loss than Xenical. This was the primary endpoint in all of the studies included for analysis.

The 2003 Cochrane review (Padwal *et al*) confirmed these findings in patients with type 2 diabetes. Compared to placebo, Xenical-treated patients lost 2.7kg (95% CI: 2.3kg to 3.1kg) or 2.9% (95% CI: 2.3% to 3.4%) more weight and patients on Reductil experienced 4.3kg (95% CI: 3.6kg to 4.9kg) or 4.6% (95% CI: 3.8% to 5.4%) weight loss. Once again, Reductil was shown to be a more effective pharmacotherapy for weight loss. Roche noted that these figures 'compared the drug treatment arms to their own individual placebo arms'. The purpose of including a placebo arm in blinded studies such as these was to enhance precision and minimise bias. In any meta-analysis of placebo-controlled trials one should always compare the effect of the intervention that was being studied with the relevant placebo arm in the same study. Once again, Roche seemed to misinterpret a key principle that underpinned evidence-based medicine.

Abbott noted that Roche had stated that neither of the two Cochrane meta-analyses concluded that Xenical or Reductil were superior in terms of weight loss. Abbott stated that the results detailed above were unambiguous and conclusive.

Abbott noted that with regard to the meta-analysis by Haddock *et al*, Roche again seemed to misinterpret the significance of comparing a treatment effect against data from the placebo arm in the same study. This was the only way to control for variations in the population included in each study. Pointing out that there were differences in mean weight loss in the placebo arm of different studies merely reinforced this point. The effect size 95% interval was the primary endpoint analysed by the authors and demonstrated that Reductil caused statistically significantly greater weight loss than Xenical.

Abbott submitted that Avenell *et al* demonstrated a trend towards increased weight loss after 12 months' treatment with Reductil vs Xenical (–4.12kg vs –3.01kg) although this did not reach statistical significance. Thus, three meta-analyses demonstrated statistically significantly greater weight loss on Reductil than Xenical and a fourth demonstrated a similar trend which did not reach statistical significance.

Abbott submitted that as discussed above, discussions around secondary endpoints analysed in these studies did not take away from the primary findings regarding weight loss in medicines that were licensed to treat obesity and whose efficacy was established by assessing their effect on body weight.

Abbott submitted that the findings from these four meta-analyses, one of which was only published earlier this year, clearly indicated that the claim at issue was based on an up-to-date evaluation of all the evidence and reflected that evidence clearly, as per Clause 7.2. The comparison was also consistent with the requirements of Clause 7.3.

Abbott noted that Roche had alleged that the claim 'Reductil is more effective than orlistat' was all-embracing in breach of Clause 7.10. Reductil was used to help obese patients lose weight as was Xenical. As discussed above, Reductil caused greater weight loss than Xenical. In all of the studies detailed on the leavepiece as well as those cited by Roche and Abbott in correspondence, the primary endpoints all related to weight loss. Furthermore, the pages preceding the claim at issue dealt either directly with efficacy in terms of weight loss or portrayed data relating to the effects that weight loss with Reductil could have on metabolic parameters. This clearly positioned such a claim as pertaining to the greater weight loss that could be achieved with Reductil. Therefore, Abbott submitted that the claim, 'Reductil is more effective than orlistat' could not be considered all-embracing and was not in breach of Clause 7.10.

PANEL RULING

The Panel noted that it had been provided with four meta-analyses regarding the pharmacological management of weight reduction (Haddock *et al*, Padwal *et al*, Avenell *et al* and Norris *et al*). All of these studies reported a greater weight loss with Reductil than with Xenical. The weight loss at one year with Xenical was 2-3.01kg and for Reductil was 3.5-5.1kg. None of the meta-analyses drew any conclusions with regard to the statistical significance of these differences; Padwal *et al* and Norris *et al* noted that the magnitude of weight loss seen with both therapies was modest. Avenell *et al* stated that although trials of Xenical showed slightly less weight loss than with Reductil, Xenical had a more beneficial effect on risk factors. Haddock *et al* noted that 'no drug, or class of drugs, demonstrated clear superiority as an obesity medication'.

The claim at issue 'Reductil is more effective than [Xenical]' was referenced to Sari *et al*. This was a short-term study and involved small numbers of patients. Weight loss at 6 months was 5.5kg (5.5%) in the Xenical group (n=30) and 10.1kg (10.2%) in the Reductil group (n=29). Although the relative efficacy of the two medicines mirrored that seen in the meta-analyses, the magnitude of the weight loss was about double that which might normally be expected.

The Panel noted that other direct comparative studies had been cited by the parties. Derosa *et al* (2005) and Derosa *et al* (2004) both failed to show any statistically significant difference between Xenical and Reductil in terms of weight loss. The Panel noted, however, that the dose of Reductil in both studies was 10mg/day and not the maximum permitted dose of 15mg/day. Kaya *et al* was another short-term study with small groups of patients which, like Sari *et al*, reported weight loss in excess of what might normally be expected (Xenical 360mg/day, n=25, –9.35kg; Reductil 10mg/day, n=22, –11.72kg, p=0.02).

The Panel noted that the meta-analyses had not reported a statistically significant difference in terms of weight loss between the two therapies. The two direct comparisons which had reported a statistically significant difference (Sari *et al* and Kaya *et al*) were short term and the absolute weight losses reported for Xenical and Reductil in each were atypical. On balance, the Panel did not consider that it had been unequivocally proven that Reductil caused more weight loss than Xenical such that the difference between the two was statistically significant as implied by the claim. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel considered that the claim 'Reductil is more effective than [Xenical]' was a broad, unqualified claim; it was unclear as to what aspect of therapy it referred. Preceding pages had detailed the effect of Reductil on HbA_{1c} and lipids. Given the unqualified nature of the claim the Panel considered that it was all embracing as alleged. A breach of Clause 7.10 was ruled.

2 Claim '86% of diabetic patients treated with Reductil 15mg demonstrated a concomitant fall in HbA_{1c} of >1%'

This claim appeared on page 3 of the leavepiece and was referenced to McNulty *et al* (2003).

COMPLAINT

Roche alleged that notwithstanding the page heading 'Weight loss with Reductil has a positive effect on HbA_{1c}', which clearly suggested that the improvement in glycaemic control was related to weight loss, the bullet point inferred that Reductil improved HbA_{1c} in the majority of diabetic patients. This clearly was misleading, particularly given evidence from clinical guidelines for type 2 diabetes published in 2001 by a collaboration between the Royal College of General Practitioners, The Royal College of Physicians and the Royal College of Nursing, which having considered data available on Reductil and Xenical, recommended only Xenical as a suitable anti-obesity medicine in the management of type 2 diabetes. This evidence was also reflected in the National Institute of Clinical Excellence (NICE) guideline on the management of blood glucose which only recommended the use of Xenical as a weight loss agent in type 2 diabetics.

Roche alleged that the footnote, 'Please note Reductil is not licensed for treatment of type 2 diabetes' suggested that it was recognized that this statement could lead to inappropriate use of Reductil to treat diabetic patients. Furthermore, McNulty *et al* referred to findings in only 68 patients receiving 15mg Reductil and the results were not in accord with the Reductil SPC which suggested that weight loss with Reductil 'was associated with a mean reduction of 0.6% in HbA_{1c}'.

Roche alleged that in summary, the claim regarding the benefits of Reductil in the treatment of type 2 diabetics was not in accord with the SPC and was not supported by the established, independent NICE guidelines on the use of anti-obesity medicines in the management of type 2 diabetes and was therefore in breach of Clause 3.

RESPONSE

Abbott noted that the claim at issue appeared beneath the heading 'Weight loss with Reductil has a positive effect on HbA_{1c}', which clearly positioned the data discussed below as relating to the effect on HbA_{1c} of weight loss due to treatment with Reductil. This was further clarified in a statement immediately beneath the claim that stated 'Please note Reductil is not licensed for treatment of type 2 diabetes'.

Abbott submitted that the page heading and the footnote, which was immediately adjacent to the claim in question, made it absolutely clear that the claim referred to data on the positive effects that weight loss with Reductil could have on HbA_{1c} when used as an aid to weight loss in patients with type 2 diabetes. This was consistent with the particulars listed in the Reductil SPC, which stated that in 'obese patients with type 2 diabetes mellitus weight loss with sibutramine was associated with mean reductions of 0.6% (unit) in HbA_{1c}'.

Abbott submitted that furthermore the quantitative effect on HbA_{1c} demonstrated in this study was in line with the SPC. In this study patients treated with Reductil 15mg (excluding those treated with 20mg which was not a licensed dose) achieved a mean

reduction in HbA_{1c} of 0.56%. In the conclusion the authors stated that 86% of the patients treated with Reductil 15mg achieved >1% reduction in HbA_{1c}. This formed the basis for the promotional claim.

Abbott submitted that these data supported the fact that 86% of diabetic patients achieving >1% reduction in HbA_{1c} was not inconsistent with a mean reduction in HbA_{1c} of 0.6% (as detailed in the SPC). This claim was therefore consistent with the particulars listed in the Reductil SPC; the company denied a breach of Clause 3.

PANEL RULING

The Panel noted that although clinical guidelines recommended the use of Xenical as part of a weight loss strategy in type 2 diabetics, they did not state that Reductil should not be used. Reductil was not contra-indicated in type 2 diabetes nor were there any special warnings or special precautions for use in such a patient population. Section 5.1 of the Reductil SPC, Pharmacodynamic properties, stated 'In obese patients with type 2 diabetes mellitus weight loss with [Reductil] was associated with mean reductions of 0.6% (unit) in HbA_{1c}'. The claim at issue '86% of diabetic patients treated with Reductil 15mg demonstrated a concomitant fall in HbA_{1c} of >1%', however, suggested a greater reduction would be seen in most patients. The Panel considered that the claim was thus inconsistent with the particulars listed in the Reductil SPC. A breach of Clause 3.2 was ruled.

Complaint received **13 July 2005**

Case completed **21 September 2005**

CASE AUTH/1739/7/05

GENERAL PRACTITIONER v NOVARTIS

Stepwise campaign

A general practitioner complained about a booklet 'Feet & Nails stamping out fungal nail infection and athlete's foot' which was part of the Stepwise campaign run by Novartis. The complainant explained that the booklet had been given to him by a patient who had requested it in response to a newspaper advertisement alerting readers to the possibility of treatment for nail infections. On receiving the booklet the patient understandably became very concerned about the potential risks from this infection and had sought treatment as suggested in the booklet. The patient was particularly concerned about the photographs on page 4 of the booklet which showed dramatic changes from fungal toenail infection.

The Panel considered that, contrary to Novartis' stated intention, most patients would assume that the photographs on page 4 of the booklet, represented the natural progression of fungal nail infection over time. The final picture of three showed a discoloured toe with a blackened toenail. The Panel noted that, aside from the colour of the nail, the colour of the toe itself was notably different in the final photograph compared with those that preceded it – dark pink/purple v normal flesh colour. There was no indication as to how long it would take for a fungal nail infection in its early stages (photograph 1) to proceed to a moderately infected nail (photograph 2) and from there to become severely affected (photograph 3). Given the appearance of the toe and nail in the final photograph the Panel could understand why some patients might become alarmed and assume that their own toe(s) would show a similar decline if left untreated. The Panel considered that without adequate explanation as to the chances of the toe, and not just the nail, becoming so badly affected, the final photograph on page 4 was alarmist and thus unbalanced in that regard. The Panel ruled a breach of the Code.

A general practitioner complained about the booklet 'Feet & Nails stamping out fungal nail infection and athlete's foot' (ref LAM04002136 April 2004) provided as part of the Stepwise campaign by Novartis Pharmaceuticals UK Ltd.

COMPLAINT

The complainant explained that the booklet had been given to him by a patient who had requested it in response to a newspaper advertisement. The complainant understood that the advertisement had alerted the patient to the possibility of treatment for nail infections and on receiving the enclosed leaflet she had understandably become very concerned about the potential risks from this infection and had sought treatment as suggested in the booklet. The patient was particularly concerned about the photographs on page 4 of the booklet which showed dramatic changes from fungal toenail infection.

The complainant alleged that this form of promotion was in breach of Clause 20.2 of the Code. The complainant did not consider that the booklet presented a balanced view and that it therefore breached the Code.

Novartis was asked to respond in relation to the requirements of Clause 20.2.

RESPONSE

Novartis submitted that the Stepwise programme, which first appeared in 1995, was designed to address research indicating that there was a large untreated reservoir of patients in the community who did not recognise that they had a fungal infection or who had

received ineffective therapy in the past which had led them to consider their condition untreatable. Fungal infection was thought to affect over a million patients in the UK at any one time, with an estimated 200,000 new patients each year. Roberts (1992) had shown that as with athlete's foot, only a small percentage of patients with fungal nail infection sought professional advice, although 80% felt that they would have done so if they had realised they were suffering from a treatable fungal infection. The materials, produced with guidance from UK dermatologists and with the support of the Society of Chiropodists and Podiatrists, were distributed to those who specifically requested them from the Novartis sponsored fungal nail infection disease awareness advertisements in the national press and on the television. Responders to the advertisements were likely to already have some concerns about nail infection, possibly fungal and were seeking advice and guidance on how to manage it. They might have noted a progression of their athlete's foot or noted a gradual deterioration of their nails as a fungal infection spread and the nail changed colour and crumbled.

On average, those who responded to the Stepwise advertisements had had their infection for 3.2 years with three or four nails affected. It was clear that by the time the patient's nails had reached this level of deterioration spontaneous resolution was not possible and successful self medication highly unlikely. Such failure might lead the patient to consider their condition untreatable. These were exactly the patients for whom the Stepwise materials were designed so as to avoid such an outcome and ensure that they received appropriate treatment and advice and wherever possible were removed from the infectious pool.

Novartis stated that the photographs on page 4 of the booklet were not intended to cause unnecessary concern, but to provide balanced and useful illustrations of the different manifestations of fungal nail infection particularly if left untreated. These photographs had been included in the Stepwise booklet since 1995 and this was the first complaint regarding their inclusion. The photographs were a fair and balanced representation of the information on fungal nail infection contained in well recognised dermatology texts such as *A Text Atlas of Nail Disorders*, (Baran *et al* 1996) and *Clinical Dermatology*, (Hunter *et al* 1995), and were similar to those appearing on patient education websites and fact sheets available elsewhere in the UK *(www.curefootpain.co.uk, www.drfoot.co.uk)*. Novartis did not consider that they caused unnecessary alarm.

Novartis submitted that the Stepwise materials had been devised to educate and encourage people to take more interest in their own healthcare and to recognise the signs and symptoms of a particular disease, which was in line with the supplementary information to Clause 20.2. The purpose of the Stepwise programme was to provide helpful information to the public about foot and nail care generally, as well as educating people who suffered from some of the common foot and nail problems, that they could be fungal in nature and thus infectious. To omit the illustrations would undermine this purpose. Written descriptions alone would not offer the same clarity.

Novartis submitted that it was impossible to predict how many patients would present with the different forms of fungal nail infection and how quickly the infection might progress as this was likely to be highly subjective and related to such issues as age, nail damage, concomitant illnesses, nature of the infection etc.

In summary, Novartis submitted that it had recognised a continuing commitment to health education of which the Stepwise programme had formed a part since 1995; over 1.4 million booklets had been distributed upon request. The purpose of the Stepwise materials was to encourage patients to take more interest and responsibility for their own health. Feedback from patients showed that the programme had raised patient awareness. Advice received from the Stepwise materials had led to patients successfully managing, with their health professional's support, long term embarrassing fungal infections using a variety of treatment options. Therefore Novartis remained confident that the Stepwise programme complied fully with the requirements of the Code.

In response to a request for more information Novartis submitted that precise details of how many patients presented with early, moderate or severe nail infections were not available. Patients who responded to the Stepwise advertisement had had their infection for 3.2 years and had three or four nails infected. At this stage the infection would have progressed beyond the mild stages but hopefully early referral and appropriate guidance would prevent progress to the more severe condition.

Novartis stated that the photographs on page 4 of the Stepwise booklet were not intended to demonstrate the progression of fungal nail infection over time, but rather to represent the spectrum of manifestation of fungal nail infection to which members of the public could relate their own infections. The rate and extent of progression of fungal nail infection depended on a number of factors including concomitant disease, pre-existing physical damage to the nail, repetitive stress damage to the nail, blood supply to the nail, speed of nail growth and the patients' general health. As stated above, the Stepwise materials, including the photographs on page 4, had been developed with the advice of the Society of Chiropodists and Podiatrists (as declared on the front of the booklet), who confirmed that the photographs appropriately reflected the condition seen by their members at different stages of fungal nail infection. Novartis provided a series of photographs of fungal nail infection taken from published sources which it stated showed a similar spectrum of manifestation of fungal nail infection to those shown on page 4 of the Stepwise booklet.

Novartis stated that most cases of untreated fungal nail infection would slowly progress to the more severe manifestations of the infection shown in the booklet where the separation of the nail from the nail bed commonly led to discolouration and inevitable loss of the affected nail. With regard to skin involvement Novartis noted that fungal nail infection was commonly preceded by athlete's foot which was caused by the same fungal organism invading the

skin between the toes. Furthermore, the same fungus which caused athlete's foot and fungal nail infection could also spread to other areas of the body. It was not unreasonable therefore for patients with the more severe nail infection to experience concomitant infection elsewhere on the body, and certainly in such close proximity to an active source of infection.

Novartis reiterated that the aim of the Stepwise programme was to offer assistance to members of the public who were sufficiently concerned about the condition of their nails to seek guidance. The inclusion of the 3 photographs rather than the more extreme manifestations of fungal infection included in academic sources was intended to assist patients in the recognition of symptoms and to encourage them to seek professional advice from a pharmacist, chiropodist, general practitioner or other health professional to confirm the diagnosis and obtain advice on treatment.

PANEL RULING

The Panel considered that, contrary to Novartis' stated intention, most patients would assume that the photographs on page 4 of the booklet represented the natural progression of fungal nail infection over time. The final picture of three showed a discoloured toe with a blackened toenail. The Panel noted that, aside from the colour of the nail, the colour of the toe itself was notably different in the final photograph compared with those that preceded it – dark pink/purple v normal flesh colour. There was no indication as to how long it would take for a fungal nail infection in its early stages (photograph 1) to proceed to a moderately infected nail (photograph 2) and from there to become severely affected (photograph 3). Given the appearance of the toe and nail in the final photograph the Panel could understand why some patients might become alarmed and assume that their own toe(s) would show a similar decline if left untreated. The Panel considered that without adequate explanation as to the chances of the toe, and not just the nail, becoming so badly affected, the final photograph on page 4 was alarmist and thus unbalanced in that regard. The Panel ruled a breach of Clause 20.2.

Complaint received **15 July 2005**

Case completed **5 October 2005**

CASE AUTH/1740/7/05 *NO BREACH OF THE CODE*

SANKYO PHARMA v BOEHRINGER INGLEHEIM

Micardis leavepiece

Sankyo Pharma explained that it had previously raised concerns with Boehringer Ingelheim about a cost comparison chart in a Micardis (telmisartan) leavepiece because it gave an inaccurate price for Sankyo's product Olmetec (olmesartan). Sankyo had not been completely satisfied with Boehringer Ingelheim's reply, nonetheless it did not complain formally under the Code. However, in April 2005, a leavepiece with the same inaccurate information was found in the offices of an out of hours' service at a hospital. Sankyo considered that Boehringer Ingelheim had breached the intercompany agreement by continuing to use the inaccurate price comparison.

The Panel noted that the leavepiece was prepared in December 2004 ie the month before the revised Pharmaceutical Price Regulation Scheme (PPRS) required an overall price reduction for a company of 7%. Companies could achieve the 7% overall price reduction by any combination of raising, lowering or maintaining prices across their product range. New prices were to be effective from 1 January 2005. In November 2004 the Authority had advised companies that they should indicate the new lower prices on promotional material as soon as possible. In the period 1 January to 31 March 2005, however, promotional material would not be considered in breach of the Code if it still carried the previously higher price. The Authority noted, however, that it would not be acceptable at any time for advertisers to compare the new lower price of their own product with the superseded higher prices of competitor products.

The Panel noted that during development of the leavepiece Boehringer Ingelheim had tried, unsuccessfully, to find out from Sankyo if the cost of Olmetec was to change. As such information had not been forthcoming the known cost of Olmetec 20mg once daily for 28 days (£14.10) had been included on the bar chart. On realising that the price of Olmetec had dropped to £12.95 Boehringer Ingelheim withdrew the leavepiece on 22 February. An email to the sales force stated that it was vital that stocks of the leavepiece were returned by no later than 4 March for destruction. On 7 March an email from the warehouse confirmed that destruction of the leavepiece was complete.

The Panel noted that Sankyo reported finding one of the leavepieces in April. Boehringer Ingelheim speculated that the leavepiece could have been left by its representative at a visit prior to it being withdrawn. There was no evidence before the Panel that it had been left since then.

The Panel noted Sankyo's allegation of a breach of undertaking. The Code required companies to comply with undertakings given under the Code. These were undertakings given to the Authority, not those undertaken informally between companies. In any event the Panel noted that Boehringer Ingelheim had denied a breach of the Code in intercompany correspondence. As Boehringer

Ingelheim had not given an undertaking to the Authority with respect to the leavepiece there could be no breach of it and the Panel ruled accordingly.

The Panel noted that the leavepiece was withdrawn within 10 working days once Boehringer Ingelheim realised that the cost of Olmetec was wrong. In that regard the Panel considered that the company had not failed to maintain high standards. No breach of the Code was ruled.

COMPLAINT

Sankyo Pharma UK Ltd noted that it had previously raised several concerns with Boehringer Ingelheim Limited about a leavepiece which it alleged was in breach of the Code. Sankyo was particularly concerned about the use of out of date and incorrect information in a bar chart which, *inter alia*, compared the cost of Micardis (telmisartan) with that of Sankyo's product Olmetec (olmesartan). Boehringer Ingelheim had replied to Sankyo and, although Sankyo was not completely satisfied with its reply, it nonetheless did not complain formally under the Code.

Sankyo now understood that the leavepiece had again been used more recently. On Saturday, 9 April 2005, a leavepiece with the same incorrect information was found on an unmanned stand in the out of hours service offices at a hospital. Access to this room was not restricted. Sankyo considered that Boehringer Ingelheim had breached the intercompany agreement by continuing to use the inaccurate price comparison in breach of Clauses 2, 9 and 22 of the Code.

RESPONSE

Boehringer Ingelheim stated that it was unclear as to which specific leavepiece this complaint referred to; it assumed that it was the leavepiece (MIC0541) which was the subject of intercompany correspondence in February 2005. Boehringer Ingelheim had addressed the points raised in a response of 10 March even though the particular leavepiece had been withdrawn from use and marked for destruction as of 22 February 2005.

With respect to the complaint now at issue, without either a copy of the leavepiece in question or a tracking code number it was difficult to comment on it being found in April 2005. Boehringer Ingelheim understood that the offices were housed in a building used as a GP surgery during the day and as an out of hours cooperative during evenings and weekends. Representatives had visited the out of hours service on 21 February and 4 April, ie once prior to and once subsequent to, the withdrawal of the leavepiece which was the subject of intercompany discussion. Without being able to identify the leavepiece Boehringer Ingelheim could not be certain as to which visit it might have stemmed from. Boehringer Ingelheim noted that the leavepiece might have been left by a GP during his/her out of hours shift.

However, with respect to leavepiece MIC0541, as stated in the correspondence from Sankyo to Boehringer Ingelheim of 25 February, the use of 'out of date and incorrect information regarding comparative costs illustrated as a bar chart' was addressed in Boehringer Ingelheim's response to Sankyo dated 10 March.

Boehringer Ingelheim noted that Sankyo had alleged a breach of Clause 22 'compliance with undertakings'. This clause was relevant to undertakings to the Authority, not intercompany correspondence. Boehringer Ingelheim reiterated that the leavepiece at issue was withdrawn prior to the intercompany dialogue and updated as necessary, and that the company had not entered into any specific agreement or undertaking as asserted by Sankyo.

By way of background Boehringer Ingelheim stated that it was aware of the guidance issued by the Authority in November 2004 about price reductions. The company maintained that the leavepiece (MIC0541) was correct at the time of final certification.

In anticipation of the introduction on 1 January 2005 of the revised Pharmaceutical Price Regulation Scheme (PPRS) the leavepiece was developed during December 2004 (ie the date of preparation). The anticipated price changes of competitor products were sought and finalised on 4 January 2005, based on the Chemist and Druggist price list. Where available, the post-PPRS prices for competitors were incorporated in the leavepiece prior to final certification and distribution. Boehringer Ingelheim noted that on several occasions it had tried unsuccessfully to get this information with respect to Olmetec (olmesartan) from Sankyo. The post-PPRS price of Olmetec was not publicly available at that time.

Boehringer Ingelheim stated that it had no reason to know of any impending change in the price of any of the competitor products, including Olmetec. Therefore, the extended development period of the leavepiece was a genuine attempt to ensure accuracy with regard to the post-PPRS price of all competitors and in good faith these were accurately reflected where these were available.

Notwithstanding the above, once Boehringer Ingelheim became aware of the revised prices of Olmetec the leavepiece was withdrawn; this was undertaken prior to the complaint. The company also provided reassurance that these revised prices would be appropriately reflected in any future Micardis promotional material.

The leavepiece (MIC0541) was withdrawn on 22 February 2005, prior to the correspondence from Sankyo. In support of this submission Boehringer Ingelheim provided confidential copies of correspondence to its field force and its warehouse.

As the leavepiece was not recalled from the health professionals to whom it had been issued, it was not possible to confirm that each and every such numbered item sent out to the field force was returned for destruction. Nonetheless the field force was instructed to return all copies of the leavepiece; all returned items were subsequently destroyed.

It was impossible to know or confirm exactly how the leavepiece was found on 9 April. Clearly it might have been left when the representative visited in February prior to its withdrawal.

Boehringer Ingelheim did not understand which sub-clause of Clause 9 'High standards, Format, Suitability and Causing Offence, Sponsorship', cited by Sankyo, was applicable. As far as the company was able to ascertain from the facts available to it, it was not in breach of Clause 9.

PANEL RULING

The Panel noted that Sankyo had only provided a one page colour photocopy of the cost comparison bar chart at issue. There was no way of knowing from what it had been copied but both parties had assumed that it was one of the pages from the leavepiece which had been the subject of intercompany correspondence in February/March 2005 (ref MIC0541).

The leavepiece was prepared in December 2004 ie the month before the revised PPRS required an overall price reduction for a company of 7%. Companies could achieve the 7% overall price reduction by any combination of raising, lowering or maintaining prices across their product range. New prices were to be effective from 1 January 2005. In November 2004 the Authority had advised, via the Code of Practice Review, that it was in the interest of advertisers to indicate the new lower prices on promotional material as soon as possible. In the period 1 January to 31 March 2005, however, promotional material would not be considered in breach of the Code if it still carried the previously higher price. The Authority noted, however, that it would not be acceptable at any time to give comparative prices in promotional material where these involved the new lower price of the advertiser's product and the superseded higher prices of competitor products.

The Panel noted that during its development of the leavepiece Boehringer Ingelheim had tried, unsuccessfully, to find out from Sankyo if the cost of Olmetec was to change. As such information had not been forthcoming the known cost of Olmetec 20mg once daily for 28 days (£14.10) had been included on the bar chart. Once Boehringer Ingelheim had realised that the price of Olmetec had dropped to £12.95 it withdrew the leavepiece. The leavepiece was withdrawn on 22 February, three days before Sankyo's first letter to Boehringer Ingelheim about the matter. An email to the sales force stated that it was vital that stocks of the leavepiece were returned by no later than 4 March for destruction. On 7 March an email from the warehouse confirmed that destruction of the leavepiece was complete.

The Panel noted that Sankyo reported finding one of the leavepieces at the offices of an out of hours service in April. Boehringer Ingelheim speculated that the leavepiece could have been left by its representative on 21 February ie the day before it was withdrawn. There was no evidence before the Panel that it had been left since then.

The Panel noted Sankyo's allegation of a breach of Clause 22 of the Code. Clause 22 required companies to comply with undertakings given under the Code. These were undertakings given to the Authority, not those undertaken informally between companies. In any event the Panel noted that Boehringer Ingelheim had denied a breach of the Code in intercompany correspondence. As Boehringer Ingelheim had not given an undertaking to the Authority with respect to the leavepiece there could be no breach of Clause 22. The Panel ruled accordingly. There was thus also no breach of Clause 2.

The Panel noted that the leavepiece was withdrawn within 10 working days once Boehringer Ingelheim realised that the cost of Olmetec was wrong. In that regard the Panel considered that the company had not failed to maintain high standards. No breach of Clause 9.1 was ruled.

Complaint received **15 July 2005**

Case completed **7 September 2005**

CASE AUTH/1741/7/05

LOCAL HEALTH BOARD PRESCRIBING ADVISOR v BAYER

Arrangements for a meeting

The prescribing advisor to a local health board alleged that Bayer had arranged a meeting at which the hospitality was not secondary to the main purpose of the evening and was disproportionate to the occasion. The complainant noted that according to the invitation one and a quarter hours of education was to be preceded by a champagne reception and followed by a gourmet dinner. The invitation stated that the venue had been highly recommended by Egon Ronay and had won numerous awards for the quality of its food. Transport to and from the meeting was offered.

The Panel noted that the complaint had been submitted before the meeting in question was held. Although the formal part of the meeting as described on the agenda was to last for only $1^1/_4$ hours, Bayer had submitted that it had in fact gone on for over 2 hours. The Panel was concerned to note from a copy of the receipt from the hotel that 38 bottles of wine and 5 individual glasses of wine had been ordered during the evening. Ten of the bottles of wine had been a French sparkling wine which the Panel assumed had been used for the 'champagne' reception. The Panel was extremely concerned about the disparity of Bayer's response on this point; while not champagne the Panel considered that 10 bottles of sparkling wine between 42 delegates was more than 'simply an offer of drinks on arrival' as submitted by Bayer. The Panel considered that the quantity of wine provided at the meeting was excessive. The total wine bill for the evening was just over £500. The Panel considered that the hospitality offered and subsequently provided was not secondary to the purpose of the meeting. In addition high standards had not been maintained and the representatives had not complied with all relevant requirements of the Code. Breaches of the Code were ruled.

The Panel considered that the invitation had sought to attract delegates to a meeting by offering them a champagne reception and a gourmet dinner at a prestigious restaurant. A breach of Clause 2 was ruled.

The prescribing advisor to a local health board complained about an invitation to a meeting issued by a representative on behalf of Bayer Healthcare. The meeting, about the medical and surgical management of erectile dysfunction, was to take place at a country house hotel. The invitation/agenda stated that the meeting would start at 18.45 with registration and a champagne reception lasting until 19.15. The formal part of the meeting consisted of two half hour presentations, one by a consultant urologist and another by a specialist nurse practitioner, which would last until 20.15. With fifteen minutes for questions and answers the formal part of the meeting finished at 20.30 with dinner. The invitation was accompanied by menus for the evening and it appeared that attendees had a free choice and could order anything from a 2 course dinner costing £15 to a 3 course gourmet dinner costing £30. The invitation stated that the restaurant had been highly recommended by Egon Ronay and had won numerous awards for the quality of its food.

COMPLAINT

The complainant stated that the invitation was forwarded to her by a general practitioner who was concerned that the accompanying dinner and preceding champagne reception did not meet the basic principles that applied under the Code. The GP considered that the dinner and champagne reception were not appropriate and were out of proportion to the occasion. The actual meeting itself was to last 1 hour and 15 minutes.

The complainant noted that menus had been included, a three course gourmet dinner menu (£30) and a three course dinner menu (£20), supposedly to aid the restaurant in the choice of food by the attendees. Within the information was the fact that the restaurant had been highly recommended by Egon Ronay and had won numerous awards for the quality of its food. Transport was also offered to and from the hotel for those that required it.

The complainant agreed with the GP that the hospitality associated with the meeting which lasted for one and a quarter hours did not appear to be secondary to the purpose of the meeting and was not appropriate and was out of proportion to the occasion.

RESPONSE

Bayer explained that the meeting was organised by a contract GP representative with the assistance of the local hospital representative.

Bayer noted that the complainant appeared to be concerned that the hotel menus were included with the invitation. The complainant also implied that this was not, as stated, to assist the hotel in preparing the evening meal. Bayer considered that this was the primary reason for asking invitees to specify their choices from the menu.

The champagne reception referred to in the invitation was simply an offer of drinks on arrival and, on reflection, would have been better worded as such. The use of the hotel's own materials with a particular typeface and the mention of Egon Ronay seemed to have given the unintended and misleading impression that the meal was not completely secondary to what was a very high quality clinical event at which the local specialist updated GPs and their support staff on an important clinical topic.

In contrast to these impressions created by the marketing aspects of the meeting, Bayer considered

that the actual costs incurred demonstrated a reasonable level of expenditure on both food and drink ie £30/head plus drinks. On the night, the clinical content of the meeting took place from 19.30 to 21.40. The presentations were held in a private room to which there was no public access.

Bayer considered that the expenditure and hospitality offered were entirely appropriate and secondary to the purpose of the meeting.

PANEL RULING

The Panel noted that the complaint had been submitted before the meeting in question was held. The complaint had thus been made on the basis of the invitation sent on behalf of Bayer. The invitation/agenda described a meeting, 'The medical and surgical management of erectile dysfunction', with one and a quarter hours' education. The formal part of the meeting was to be preceded by a champagne reception and the meeting was to end with dinner. Invitees had been sent the dinner menus, one of which was headed 'Gourmet dinner menu', and told that the restaurant was highly recommended by Egon Ronay and had won numerous awards for the quality of its food. Transport to and from the hotel was offered.

The Panel noted that although the formal part of the meeting as described on the agenda, was to last for only $1^1/_4$ hours, Bayer had submitted that it had in fact gone on for over 2 hours. This part of the meeting had taken place in a private room. Dinner was served in the dining room. The company had paid for 47 dinners although only 42 people had been at the meeting. The majority of attendees had ordered the 3 course gourmet dinner at a cost of £30 a head. The Panel asked Bayer to provide a copy of the receipt from the hotel. Bayer's original submission included a breakdown of the costs but had not included a copy of the actual receipt. The Panel was concerned to note from the copy of the receipt that 38 bottles of wine and 5 individual glasses of wine had been ordered during the evening. Ten of the bottles of wine had been Cavalier Brut, a French sparkling wine which the Panel assumed had been used for the 'champagne' reception. The Panel was extremely concerned about the disparity of Bayer's response on this point; while not champagne the Panel considered that 10 bottles of sparkling wine between 42 delegates was more than 'simply an offer of drinks on arrival' as submitted by Bayer. The Panel was also concerned that Bayer's original submission had referred to ten glasses of dry white wine at £36.50 which was inconsistent with the receipt from the hotel which listed ten bottles of Cavalier Brut at £135. The Panel considered that the quantity of wine provided at the evening meeting, to which many of the delegates would have driven, was excessive. The total wine bill for the evening was just over £500. The Panel considered that the hospitality offered and subsequently provided was not secondary to the purpose of the meeting. The Panel ruled a breach of Clause 19.1 of the Code. The Panel considered that high standards had not been maintained and that the representatives had not complied with all relevant requirements of the Code. Breaches of Clauses 9.1 and 15.2 were ruled.

The Panel noted that Clause 2 of the Code stated that, *inter alia*, activities associated with promotion must never be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. A ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel considered that the invitation was such as to warrant a ruling of a breach of this clause; it had sought to attract delegates to a meeting by offering them a champagne reception and a gourmet dinner at a prestigious restaurant. A breach of Clause 2 was ruled.

Complaint received **18 July 2005**

Case completed **19 August 2005**

CASE AUTH/1742/7/05

PRIMARY CARE TRUST HEAD OF MEDICINES MANAGEMENT v MERCK

Conduct of representative

The head of medicines management at a primary care trust (PCT) complained about the manner in which a representative from Merck had promoted Niaspan (nicotinic acid) at a general practice within the PCT. The general practitioner granted him access to the practice database from which the representative identified patients with a recorded high density lipoprotein (HDL) level < 1mmol/l. The representative took away the names and addresses of those patients and sent them a letter, a copy of which was provided. Many patients who received the letter did not understand its content, and queried its source and purpose with reception staff who were equally in the dark, the GP not having informed them of this initiative.

The complainant considered that the activities of the representative were questionable, particularly in relation to the access and removal from the practice of confidential patient information (albeit with the approval of the GP).

The Panel noted that the representative had acted independently of any instruction or briefing, and, of his own volition, had offered to help with a search and review of patient records. It was not a company sponsored audit. There was no formal documentation. The representative searched the practice computer and identified approximately 40 patients with low HDL-cholesterol for review. An unsigned letter, dictated by the GP, was produced and sent to the patients by the representative. Patients had been confused by the letter. The complainant alleged that the representative had taken the patients' names and addresses from the practice. The company had not commented on this point. The Panel did not accept the company's submission that the representative's actions on this occasion were totally out of character; he had instigated similar reviews at four other practices and thus such activity appeared to be part of his normal working practice.

The Panel considered that this was an extremely serious matter. The representative had, with the GP's permission, reviewed the practice database and accessed patient records. There was no written documentation. The representative had not maintained a high ethical standard and complied with all the requirements of the Code. High standards had not been maintained. Breaches of the Code were ruled. The Panel considered that the representative's conduct had bought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The head of medicines management at a primary care trust (PCT) complained about the activities of a representative from Merck Pharmaceuticals UK.

COMPLAINT

The complainant noted that the representative had promoted Niaspan (nicotinic acid) at a general practice within the PCT. The general practitioner granted him access to the practice database which the representative then searched for all patients who had a recorded high density lipoprotein (HDL) level < 1mmol/l. The representative took from the practice the names and addresses of those 40 patients and sent them a letter, a copy of which was provided.

Many patients who received the letter did not understand its content, and queried its source and purpose with reception staff who were equally in the dark, the GP not having informed them of this initiative.

The complainant considered that the activities of the representative were questionable, particularly in relation to the access and removal from the practice of confidential patient information (albeit with the approval of the GP).

When writing to the company the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2 and 18.1 of the Code.

RESPONSE

Merck stated that it regrettably acknowledged that the events described above did occur; it had been unaware of them prior to receiving the complaint. The representative admitted he had conducted a therapy review at a practice within the complainant's area.

The representative had discussed Niaspan with the GP in March 2005. Niaspan was indicated for use with a statin to treat dyslipidaemia and was of benefit in raising HDL-cholesterol, an independent risk factor for cardiovascular disease. There had been a recent amendment to the summary of product characteristics, a copy of the version in use at the time of this meeting was provided.

During the discussion the GP stated that although he wanted to treat patients with low HDL-cholesterol, as a single-handed practice his staff were too busy to search and review patient records to identify those with a low HDL-cholesterol and so the representative offered to help. The GP agreed to this and a computer at the practice was made available to the representative a fortnight later. Although the GP was in the room throughout, the representative was given access to the search facility of the computer system and he proceeded to search for patients with a recorded HDL-cholesterol level < 1mmol/l. This was a verbal agreement so there was no formal documentation.

The representative returned to the practice a week later to discuss the findings of the search with the GP. He had identified approximately 40 patients with a low HDL-cholesterol for review. The GP agreed to recall these patients to discuss their treatment options; however he again indicated that his staff were too

busy to do the letters and the representative offered to help. The GP agreed to this offer but again this was a verbal agreement and there was no documentation.

The GP dictated a short letter of recall that could be sent to the patients. At this stage the representative printed off the names and addresses of the patients that had been saved in the search the previous week. He produced the letters, put them into envelopes and posted them. Although the letters included the practice address and the GP's name, the GP did not sign the letters. No originals of this letter were available but a copy of the letter sent to all the patients concerned was provided.

The representative had no further involvement with this review once the letters had been posted. However, during a later conversation, the GP told the representative that he had been told not to proceed with the review by the PCT. The GP admitted that the PCT had contacted him after a patient had complained to the patient advisory liaison service about the letter. The GP had explained to the PCT what had happened and had thought that was the end of the matter.

The representative was not involved in a company-sponsored audit but had acted under his own volition. The representative acknowledged that he had acted independently of any instructions or briefing he had received. He also acknowledged he had done wrong as he knew he should not have accessed or looked at patient information. He had acted with the best intentions to help the GP and rather naively thought that as the GP had agreed to him performing the search there would be no repercussions. The representative also admitted that he had instigated similar reviews at four other practices although his degree of involvement had varied. During his time with Merck the representative in question had had an unblemished record until now. His behaviour and actions on this occasion were out of character.

In view of the representative's actions Merck regrettably accepted a breach of Clauses 9.1 and 15.2 as the representative did not maintain a high ethical conduct and comply with all aspects of the Code; thus the company had to accept that high standards had not been maintained at all times.

Merck did not accept there was a breach of Clause 18.1. The GP had decided that he wanted to review the treatment of his patients at high cardiovascular risk with low HDL-cholesterol. Although the representative had helped identify patients with low HDL-cholesterol for review there was no agreement that in return the GP would prescribe them Niaspan. Thus there was no inducement to prescribe, merely help to identify patients potentially at high cardiovascular risk with the view to improving their care.

Furthermore Merck did not believe that the failings of a single representative, who was experienced and knowledgeable of the Code, should be sufficient to rule a breach of Clause 2.

Merck considered the actions of this representative were very serious and had initiated disciplinary proceedings.

In addition, as the concept of patient reviews had emerged since the introduction of the general medical services contract as a method of helping general practitioners to achieve targets for the receipt of quality payments, Merck had sent all primary care representatives a briefing to ensure that if any of their practices wished to conduct a review that they did not become directly involved. A copy of this briefing was provided.

PANEL RULING

The supplementary information to Clause 18.1 of the Code provided, *inter alia*, that if medical representatives provided medical and educational goods and services then this must not be linked in anyway to the promotion of products. Neither the company nor its medical representatives might be given access to data/records that could identify, or could be linked to, particular patients.

The Panel noted that the representative had acted independently of any instruction or briefing, and, of his own volition, had offered to help with a search and review of patient records. It was not a company sponsored audit. There was no formal documentation. The representative searched the practice computer and identified approximately 40 patients with low HDL-cholesterol for review. An unsigned letter, dictated by the GP, was produced and sent to the patients by the representative. Patients had been confused by the letter. The complainant alleged that the representative had taken the patients' names and addresses from the practice. The company had not commented on this point. The Panel did not accept the company's submission that the representative's actions on this occasion were totally out of character; he had instigated similar reviews at four other practices and thus such activity appeared to be part of his normal working practice.

The Panel considered that this was an extremely serious matter. The representative had, with the GP's permission, reviewed the practice database and accessed patient records. There was no written documentation. In that regard the criteria set out in the supplementary information to Clause 18.1 had not been complied with; a breach of Clause 18.1 was thus ruled. The representative had not maintained a high ethical standard and complied with all the requirements of the Code. High standards had not been maintained. Breaches of Clauses 9.1 and 15.2 were ruled. The Panel considered that the representative's conduct had bought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

During its consideration of this case the Panel noted that the representative had searched the practice database, identified patients and sent them a letter all with the agreement of the GP. Customers' requests or wishes, however, could only be met if the resultant actions were within the requirements of the Code.

Complaint received **19 July 2005**

Case completed **16 September 2005**

CASE AUTH/1744/7/05

HOSPITAL LEAD PHARMACY TECHNICIAN v ASTRAZENECA

Conduct of representative

A hospital lead pharmacy technician complained that an AstraZeneca representative had given peak flow meters directly to nursing staff on wards in contravention of hospital policy.

The Panel noted that the peak flow meters left by the representative were promotional aids. The chief pharmacist considered them to be medical equipment.

The Panel noted that the representative was unaware that the hospital policy was such that representatives were not allowed to leave promotional samples with staff on wards/departments without having first discussed the matter with main stores, pharmacy, estates or catering as appropriate. A form of indemnity had to be completed before the supply of equipment, samples or consumable goods. It appeared from AstraZeneca's submission that the health professions were also unaware of the policy. Nonetheless the representative had failed to comply with the policy; a breach of the Code was ruled. Given the circumstances, the Panel did not consider that the representative or the company had failed to maintain a high standard. No breach of the Code was ruled in that regard.

COMPLAINT

A lead pharmacy technician at a hospital stated that an AstraZeneca representative had given free peak flow meters directly to nursing staff on wards. This practice was not authorized either by the pharmacy department or the main hospital stores. Furthermore, the peak flow meters were faulty and gave false readings.

When writing to AstraZeneca the Authority asked it to comment in relation to Clauses 7.2, 9.1, 15.2 and 15.4 of the Code.

RESPONSE

AstraZeneca stated that its representative had held a lunchtime meeting at the hospital to promote Symbicort (formoterol, budesonide). The meeting, attended by four doctors and two nurses, was held in a private room adjacent to the medical assessment ward. The representative gave a presentation and provided a sandwich lunch. On the promotional stand there were pens, leavepieces, post-it notes and a peak flow meter that could be requested by the attendees. At the end of the meeting one of the doctors asked for a number of peak flow meters as they would be useful for the ward nursing team. The peak flow meters were branded with the Symbicort logo and cost £3.25 each. The representative dropped off two of these peak flow meters at the nursing station a few days later and gave them to the nurses who gratefully accepted them.

Following this complaint an investigation was conducted into details of the hospital's policy with regard to how pharmaceutical companies conducted their business within the hospital and trust. According to the hospital's deputy chief pharmacist the policy stated that representatives must never leave promotional samples with staff on wards or departments. Any promotional material that representatives wanted to leave must be discussed with the relevant purchasing and supply department ie main stores, pharmacy, estates and catering beforehand. The policy also highlighted that in order to fulfil the policy, all trust staff must adhere to the policy. No goods or services might be procured through individual staff agreement with company representatives. It was the responsibility of individual members of staff to ensure that any representatives visiting them, for the purpose of promoting business with the trust, adhered to the policy.

The representative reported that on handing over the two peak flow meters neither the medical staff during the lunch time meeting nor the ward nursing staff indicated that there was a specific hospital policy on receiving promotional samples or other materials from representatives. A telephone interview with the ward sister and the respiratory hospital consultant revealed that they were not aware of this specific hospital policy or any policy relating to receiving peak flow meters from representatives. A letter from the consultant chest physician indicated clearly that his hospital unit was unaware of any such trust policy on the provision of such items to hospital staff.

Two months later, the doctor who had requested the peak flow meters at the lunchtime meeting told the representative that one of the peak flow meters had given an incorrect reading of 150 l/min compared to another peak flow meter on the ward supplied by the hospital. The representative asked for both of the peak flow meters to be returned so that they could be sent to AstraZeneca head office for testing. However the supposedly faulty peak flow meter had already been thrown away by nursing staff. The remaining unused peak flow meter was returned to AstraZeneca for an interim check.

AstraZeneca submitted that the representative had acted responsibly and demonstrated high standards by attempting to retrieve the peak flow meters so that they could be tested by head office staff before formal testing by the manufacturer. The representative was unaware of hospital policy regarding the prohibition of handing out peak flow meters to members of staff, as were the hospital staff that requested and accepted them as indicated by a letter from the consultant.

The representative did not knowingly or purposely break any hospital policies; he acted responsibly

throughout and maintained a high standard of ethical conduct in the discharge of his duties.

AstraZeneca regretted that this matter had prompted a complaint and would have welcomed direct contact from the hospital pharmacy department to enable it to investigate and comply with their local policies. Not all hospital trusts had such policies in place and where they did exist AstraZeneca reasonably expected that the trust would tell the company so that representatives could comply with them.

AstraZeneca denied breaches of Clauses 7.2, 9.1, 15.2 and 15.4 of the Code in relation to the conduct of this representative.

FURTHER COMMENTS FROM THE COMPLAINANT

Following a request to the complainant for further comments a response was received from the chief pharmacist, who provided a copy of the policy, procedure and guidelines in place at the hospital. The chief pharmacist noted that the guidance included a section entitled 'Notice to all representatives and agents' which was freely available to all company representatives on request. Paragraph 5 referred to the position regarding samples of products.

The chief pharmacist was on leave at the time of the incident and had therefore read through the correspondence associated with it on his return. Having considered in particular the letter from AstraZeneca, he was satisfied that there appeared to have been a genuine misunderstanding of the policy regarding provision of medical equipment (ie peak flow meters) and on behalf of the hospital trust he did not feel that any further action against either AstraZeneca or the representative was appropriate.

PANEL RULING

The Panel noted the request from the chief pharmacist that further action was not appropriate. Under Paragraph 15.1 of the Constitution and Procedure a complaint could be withdrawn only up until such time as the respondent company's comments had been received, but not thereafter. Thus the complaint had to proceed.

The Panel noted that Clause 15.4 required that the arrangements in force at any particular establishment must be observed. It appeared that the health professionals were not aware of the policy. The policy stated in paragraph 2.5 that representatives 'must never leave promotional samples with staff on wards/departments' and that any promotional material that representatives wanted to leave must be discussed with the purchasing and supply department for that product ie main stores, pharmacy, estates and catering beforehand. A form of indemnity had to be completed before the supply of equipment, samples or consumable goods. The document 'Notice to all representatives and agents' referred in paragraph 5 to samples of products which must not be left with ward/department staff and stated that any samples to be left by representatives had to be discussed via the relevant purchasing and supply department. Pharmaceuticals would go through pharmacy, medical and surgical goods via main stores. The documents were dated January 2005.

The Panel noted that the peak flow meters left by the representative were promotional aids. They were not samples of medicines. The Panel noted that the chief pharmacist considered them to be medical equipment.

The Panel noted that the representative was unaware of the policy documents. It appeared from AstraZeneca's submission that the health professionals were also unaware of the policy documents. The Panel considered nevertheless that the representative had failed to comply with the policy documents. Thus it ruled a breach of Clause 15.4 of the Code.

The Panel considered that the policy documents might benefit from more clarity as to the exact arrangements.

Taking all the circumstances into account, the Panel did not consider that the representative or the company had failed to maintain a high standard. No breach of Clauses 9.1 and 15.2 was ruled.

Complaint received **19 July 2005**

Case completed **12 October 2005**

CASE AUTH/1746/7/05

LOCAL HEALTH BOARD PRESCRIBING ADVISER v TRINITY-CHIESI

Conduct of representatives

A prescribing adviser complained about the conduct of representatives from Trinity-Chiesi stating they had approached practices in the locality to suggest changes to medicines which they stated had been approved by the local health board. The complainant was not aware that the local health board had met any representative from the company, and the prescribing team had not approved any such changes. This behaviour was both inappropriate and unacceptable, and the complainant was very angry and disappointed that practices had been misled in this way.

The local health board considered that some of the changes proposed were potentially detrimental to patients. These switches might also have a negative effect on a practice's generic rate, a target which they worked hard to achieve. The local health board would therefore not support the proposed changes and had advised practices to contact it before working in partnership with Trinity-Chiesi or any other company.

The Panel noted that the parties' accounts differed. It was difficult in such circumstances to determine where the truth lay.

According to one practice whilst the representative did not explicitly state that the local health board endorsed the switches, he did say that it would be happy with the cost savings and thus gave the impression that it supported the company's work. According to the second practice the representative had stated that the local health board was fully behind the company. The representative and the company denied the allegations.

Given the parties differing accounts it was difficult to determine precisely what had been said. Nonetheless, two practices had been left with the impression that the local health board supported the company's work and that was not so. In the Panel's view it was beholden upon representatives to be abundantly clear when explaining or referring to the position of a local health board in relation to any activity to ensure that a misleading impression was not given. Representatives should be aware that the mere mention of a local health board, or the like, in a conversation about a product or service might lead people to draw their own conclusions. If representatives referred to such bodies they must also be abundantly clear about the position of that body with regard to the matter under discussion. Given the involvement of two practices the Panel considered that the balance of probability was that the representative had not been sufficiently clear about the position of the local health board and had given a misleading impression in this regard. The representative had not maintained a high standard of ethical conduct. Breaches of the Code were ruled.

The Panel decided not to rule a breach of the Code with regard to high standards as the matter was adequately covered by its ruling above. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.

A prescribing adviser complained about the conduct of representatives from Trinity-Chiesi Pharmaceuticals Ltd.

COMPLAINT

The complainant stated that the local health board had noted that representatives from Trinity-Chiesi had approached local practices to suggest changes to medicines which they stated had been approved by the local health board. The complainant was not aware that the local health board had met any representative from the company, and the prescribing team had not approved any such changes. This behaviour was both inappropriate and unacceptable, and the complainant was very angry and disappointed that practices had been misled in this way. Breaches of Clauses 7.2 and 15.2 were alleged.

The local health board considered that some of the changes proposed were potentially detrimental to patients. These switches might also have a negative effect on a practice's generic rate, a target which they worked hard to achieve. The local health board would therefore not support the proposed changes and had advised practices to contact it before working in partnership with Trinity-Chiesi or any other company.

When writing to Trinity-Chiesi, the Authority asked it to respond in relation to Clauses 2 and 9.1 of the Code in addition to Clauses 7.2 and 15.2 referred to by the complainant.

RESPONSE

Trinity-Chiesi stated that it was extremely concerned to learn that the local health board believed that its representatives had acted improperly.

The representative's role was to promote the Trinity-Chiesi product portfolio within primary care; this contained a wide range of low-cost medicines across a range of therapy areas. The emphasis was on providing high quality medicines which could help practices save on current prescribing costs, without compromising patient care. There had been no previous complaints or concerns about his performance or approach and his manager stated that he was recognised by his customers as consistently going about his work in a professional manner.

With regard to training on the Code, the representative participated in a company-wide training programme in May 2004 which took the form of a one hour presentation on the application of the Code to field based activities by Trinity-Chiesi's consultant medical director and was followed by a

written multiple-choice assessment, which he passed. In addition he recently received further training on Code of Practice issues with the use of third party endorsements in May 2005, in the form of a presentation to the regional business team by the regional business manager. This presentation was made in response to a request from the head of sales that all regional managers to remind their representatives about what they could and could not say in the context of endorsements and compliance with the Code. There had been no previous concerns raised in the area involved.

The representative and his manager could not explain the complainant's comments. The representative was certain that he had never stated or implied to a customer that any change of treatment had been endorsed by the local health board, and that he believed he always worked in accordance with the requirements of the Code. This view was supported by his manager. If asked the opinion of the local health board the representative was adamant he always advised customers to ask the board direct, in line with the training he had received. He had never met the complainant but had spoken to her in January of this year with a view to arranging a meeting. He had had some recent correspondence with the local health board. Trinity-Chiesi noted that the representative's letter to the local health board was certificated, supporting his assertion that he operated in line with company guidelines. His meeting with the complainant had been deferred in view of the current complaint.

In summary, Trinity-Chiesi could not find any evidence to support the complainant's concerns. The representative in question was an exemplary performer. His manager stated that he maintained high standards and worked within the Code at all times in line with Clause 15.2. Consistent with this, the representative denied breaching Clause 7.2 by misleading customers about the views of the local health board. Trinity-Chiesi firmly believed that both the representative and the company had maintained high standards at all times and had not breached Clause 9.1 of the Code.

Trinity-Chiesi strongly refuted any suggestion that its current activities or materials might bring discredit upon, or reduce confidence in the industry as a whole (Clause 2).

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that the company's submission that the representative was certain that he had never stated or implied to a customer that any changes in treatment had been endorsed by the local health board and that he always advised the customer to ask the board direct conflicted with information obtained from two practices.

The first practice, which wished to remain anonymous so as not to jeopardise future partnership working with the pharmaceutical industry confirmed that although the representative did not explicitly state that the local health board was endorsing the switches, he did state that the local health board would be very happy with the cost savings that the switches would achieve. This left the practice with the impression that the local health board supported the company's work. The complainant noted that the local health board was not always in agreement with cost saving initiatives. There were many other issues to consider, such as generic rates and future drug tariff cost reductions, and it would be incorrect for representatives to assume and inform practices that the local health board always endorsed cost saving switches.

The complainant submitted that a practice manager at a second practice had stated that when it was suggested that the practice might contact the local health board for approval, the representative clearly stated that the local health board was fully behind the company, had met previously with the local health board which was happy with the way that the company worked.

In relation to the statement that the emphasis was on providing high quality medicines which could help practices save on current prescribing costs, without compromising patient care, after careful consideration of the proposed switches, the complainant considered that this was not the case for every medicine suggested. Some of these switches contradicted the prescribing messages that the local health board provided to practices, and therefore might have the potential to compromise patient care.

PANEL RULING

The Panel noted that the parties' accounts differed. It was difficult in such circumstances to determine where the truth lay.

According to one practice whilst the representative did not explicitly state that the local health board endorsed the switches, he did say that it would be happy with the cost savings and thus gave the impression that it was in support of the company's work. According to the second practice the representative had stated that the local health board was fully behind the company. The representative and the company denied the allegations.

Given the parties differing accounts it was difficult to determine precisely what had been said. Nonetheless, two practices had been left, with the impression that the local health board supported the company's work and that was not so. In the Panel's view it was beholden upon representatives to be abundantly clear when explaining or referring to the position of a local health board in relation to any activity to ensure that a misleading impression was not given. Representatives should be aware that the mere mention of a local health board, or the like, in a conversation about a product or service might lead people to draw their own conclusions. If representatives referred to such bodies they must also be abundantly clear about the position of that body with regard to the matter under discussion. Given the involvement of two practices the Panel considered that the balance of probability was that the representative had not been sufficiently clear about the position of the local health board and had given a misleading impression in this regard. The

representative had not maintained a high standard of ethical conduct. Breaches of Clauses 7.2 and 15.2 were ruled.

The Panel decided not to rule a breach of Clause 9.1 of the Code as the matter was adequately covered by its ruling of a breach of Clause 15.2. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of special censure and reserved for such use.

Complaint received **26 July 2005**

Case completed **22 September 2005**

CASE AUTH/1747/7/05

PFIZER/DIRECTOR v LILLY

Use of clinical paper to promote Cialis

Pfizer alleged that Lilly's use of von Keitz *et al* (2004) to promote Cialis (tadalafil) was in breach of the Code based on the ruling in Case AUTH/1578/4/04 and also in breach of its undertaking given in that case. The latter aspect of the complaint was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Code of Practice Appeal Board.

Von Keitz *et al* reported a patient preference study comparing tadalafil with sildenafil for the treatment of erectile dysfunction. Pfizer was concerned that the comparison of the maximum dose of tadalafil with the lower dosages of sildenafil meant that the data were meaningless to establish true patient preference. Pfizer alleged that in this regard the data was misleading. Pfizer was also concerned that the dosing instructions provided to those taking tadalafil (that they may find their sex life is more flexible and less planned). Pfizer considered that this statement favoured tadalafil; positive assumptions would be made about the product which would result in patients expressing a preference for that treatment.

Pfizer noted that the discussion section of von Keitz *et al* highlighted the study's major limitations; nonetheless the company considered that the paper should not be used to promote Cialis. The abstract of the paper made a clear conclusion which did not represent the limitations. Health professionals, particularly those without specific expertise in erectile dysfunction studies, would be unable to tease out the limitations and could easily be misled from reading the conclusions in the abstract.

The Panel noted that Case AUTH/1578/4/04 concerned a folder entitled Patient Preference Studies issued by Lilly. The claim 'Patients preferred Cialis 20mg over sildenafil 50mg' and '90% of men who had previously used sildenafil 25-100mg chose to use Cialis [20mg] in the study extension for the treatment of their ED' were ruled to be unfair comparisons in breach of the Code. The relevant studies were Ströberg *et al* and Govier *et al*. The material now at issue was a reprint of another study, von Keitz *et al*, which had been made available from a promotional stand. On balance the Panel considered that the material and circumstances in the case now before it, Case AUTH/1747/7/05, were sufficiently different to those in Case AUTH/1578/4/04 such that there was no breach of undertaking. The Panel ruled no breach of the Code.

The Panel noted that von Keitz *et al* had been made available from a promotional stand and Lilly's submission that prescribing information had been attached to the paper.

The Panel noted that although the discussion section of von Keitz *et al* clearly detailed the limitations of the study, and the paper was followed by two critical editorials, the paper nonetheless stated that 73% of patients preferred tadalafil compared with sildenafil. The use of the paper in a promotional context meant that this comparative statement was, in effect, a claim for Cialis v Viagra which was qualified by the small print in the rest of the paper. One of the editorials stated that the defects in the study design limited its applicability to the general population and that further studies with better designs were needed before any firm conclusions could be drawn.

The Panel considered that the use of von Keitz *et al* to promote a patient preference for Cialis v Viagra was misleading. Breaches of the Code were ruled.

Pfizer Limited complained about the use of von Keitz *et al* (2004) by Eli Lilly and Company Limited to promote Cialis (tadalafil). Pfizer supplied Viagra (sildenafil). Both products were phosphodiesterase type 5 (PDE5) inhibitors that were taken orally for the treatment of erectile dysfunction.

Inter-company correspondence had failed to resolve the issues.

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

COMPLAINT

Pfizer alleged that Lilly's use of von Keitz *et al* was in breach of the Code based on the ruling in Case AUTH/1578/4/04. Lilly had used the paper at a meeting of the Sexual Dysfunction Association in May 2005, although it was conceivable that it had also been used more widely.

Von Keitz *et al* reported yet another patient preference study comparing tadalafil with sildenafil. As noted in Case AUTH/1578/4/04, Pfizer had many concerns

about these types of study and the true meaning of them for the use in promotion of Cialis.

Pfizer was concerned about:

a) The inappropriate comparison of the maximum dose of tadalafil with the lower dosages of sildenafil.

Pfizer stated that these data were meaningless to establish true patient preference if the highest dosage of one was used and compared to differing and lower dosages of a comparator. Pfizer alleged that this type of data should not be used as promotional material as they represented an incorrect comparison of two treatments and were therefore misleading.

b) The dosing instructions provided to those taking tadalafil were that 'they may find their sex life is more flexible and less planned'.

Pfizer considered that this statement favoured tadalafil as assumptions were made about the product, which attributed positive messages about the treatment. Pfizer considered this would result in patients expressing a preference for this treatment.

c) The limitations of these studies (as acknowledged by the authors) for use as promotional material. Pfizer considered that the conclusions would mislead health professionals.

All of these concerns applied to von Keitz *et al*. Pfizer noted that the detailed discussion section of the paper clearly highlighted the study's major limitations; nonetheless the company considered that the paper should not be used to promote Cialis. The abstract of the paper made a clear conclusion which did not represent the limitations. Health professionals could easily be misled from reading the abstract which did not refer to some serious limitations of the study. Pfizer was concerned that without specific expertise in erectile dysfunction studies many health professionals would be unable to tease out the limitations and would be misled by the conclusions in the abstract.

The meaning of preference studies had been debated at international scientific meetings and the general consensus was that they provided widely varying results with dubious scientific meaning; Pfizer had been advised this at its expert advisory board meetings for some time. Pfizer's concerns about these preference studies were clearly supported by the ruling in Case AUTH/1578/4/04.

Pfizer was concerned that Lilly had continued to provide health professionals with these data as a means of promoting Cialis. Pfizer alleged that as well as breaches of the Code outlined in Case AUTH/1578/4/04 (Clauses 7.2 and 7.3) the use of this material was in a breach of Clause 22.

In inter-company correspondence Lilly had acknowledged all the limitations of the study (ie dosing comparison, biased dosing instructions and use as promotional material). Lilly had stated that all of the limitations of the study were in the discussion section of the paper and that it had provided its salesforce with a detailed briefing document in which they would have to communicate the limitations of the study and encourage doctors to read the ***whole*** paper. Pfizer noted that when it obtained this paper this did not happen. Lilly also stated that it did not use any of the claims in this paper as part of its stand.

In fact, Pfizer was at odds to understand Lilly's letter to it, which clearly understood and commented on the major study limitations with open acknowledgement that the salesforce would need specific training on this and a briefing document. Lilly also acknowledged that no ideal preference study existed. This in Pfizer's opinion reinforced its concerns on the use of this paper and these type of studies overall.

When writing to Lilly, the Authority asked it to respond in relation to Clauses 2 and 9.1 of the Code in addition to Clauses 7.2, 7.3 and 22 referred to by Pfizer.

RESPONSE

Lilly noted that sildenafil was available in tablets of 25mg, 50mg and 100mg; the licensed starting dose was 50mg. Tadalafil was available in tablets of 10mg and 20mg and the licensed starting dose was 10mg.

Von Keitz *et al*, published in European Urology, was a multicentered, double-blind, placebo controlled, crossover study which had evaluated patient preference between tadalafil and sildenafil. Eligible patients were randomised to either sildenafil 50mg with sildenafil instructions, tadalafil 20mg (with either tadalafil or sildenafil instructions) or placebo (with either tadalafil or sildenafil instructions). No patients were actually randomised to the placebo treatment arm but the use of this arm maintained physician and patient blinding. Von Keitz *et al* was one of the first studies to assess patient preference and employ a methodology to enhance blinding for erectile dysfunction (ED) medicine with different dosing instructions.

After four weeks of treatment, all patients with sildenafil instructions were offered upward dose titration. 35% of the study population taking sildenafil were escalated to the 100mg maximum dose. This limit of 35% 'was imposed in order to mimic the pattern of dose usage observed in clinical practice'. Patients taking sildenafil who requested titration but were 'denied' and patients taking tadalafil 20mg (but following sildenafil instructions) were given identical placebo tablets to maintain blinding.

Patient preference was assessed by the patient's blinded choice of which treatment they chose to continue in the extension phase of the study. Overall 73% chose to continue on tadalafil 20mg compared to 27% who chose to continue on sildenafil (50mg or 100mg). The authors noted that titration did not affect patient preference and subgroup analysis of patients on maximum dose sildenafil (100mg), randomised dose sildenafil (50mg) and patients who were 'denied' upward titration of sildenafil were conducted. Comparison of patients on maximum dose therapies resulted in 69% of patients choosing to continue on tadalafil 20mg compared with 31% on sildenafil 100mg. Preference results in patients who did not request titration of sildenafil showed a 74% preference for tadalafil. Statistical analysis of preference required significance at the 0.05 level in order to reject the null hypothesis. This was achieved for all three comparisons. Lilly therefore concluded that appropriate dose comparisons were available

within von Keitz *et al*. Results of preference analysis for each of the three dose comparisons was presented in graphic form, alongside the overall preference result in the paper, and also in the text of the results section relating to patient preference.

Blinding was maintained throughout the study and so the issue of the actual dose of medicine taken by patients might be considered of secondary importance compared to comparisons of 'efficacious doses' of a medicine. Some patients (n=74) randomised to sildenafil 50mg considered that it was sufficiently efficacious and therefore did not request upward titration. Therefore, comparison between sildenafil 50mg and tadalafil 20mg in this case compared 'efficacious doses' of each medicine. Such comparison was of scientific merit.

Comparison of tadalafil 20mg and sildenafil patients who were 'denied' upward titration was the only comparison with obvious bias. Again these patients remained blinded to the fact that upward titration was denied and received an identical placebo tablet. Upward titration of sildenafil was 'denied' in 34 of the 181 patients who completed the study.

The limitation concerning the 35% capping of sildenafil titration was highlighted in the discussion section of the paper and in the conclusion section. However, the authors reaffirmed the overall result of the study, which was supported with the evidence that similar ratios of patient preference for tadalafil were seen in all three subgroups of sildenafil users including those on maximum dose therapy. Again this limitation was discussed in detail in both editorial comments, which were attached to the paper.

Tadalafil 10mg was not used in the study design. Von Keitz *et al* reported the results of a study conducted in the US, Spain and Germany, between January and September 2002. Tadalafil was launched in Europe in 2003. It was stated in the discussion section of the paper that 'When the study was designed, tadalafil 20mg was proposed as the recommended starting dose for ED treatment'. The discussion section of the paper and the Montorsi editorial noted that 10mg was the recommended starting dose in some countries and as mentioned above the European prescribing information was attached to the paper.

Lilly therefore refuted Pfizer's allegation that von Keitz *et al* was scientifically 'meaningless' and misled health professionals because of an 'inappropriate comparison of maximum dose tadalafil with the lower doses of sildenafil'. This conclusion was supported by the reasons discussed above. Most significantly, there was evidence within the paper of appropriate comparisons at the maximum dose of each medicine. In addition, while the trial design did not provide appropriate comparisons at the starting doses, the overall result was supported by the fact that similar results were seen on analysis of the individual sildenafil doses and blinding of dose escalation was maintained. Furthermore, any potential limitations secondary to the dosages used in the trial design were made clear numerous times throughout the paper and in the accompanying editorials.

Lilly stated that a blinded comparison of two medicines with different pharmacokinetic properties and hence different dosing instructions was challenging. In von Keitz *et al*, patient and physician blinding was maintained using a sham placebo arm as noted above. Indeed, it was one of the first double-blind studies assessing patient preference between two PDE5 inhibitors with different pharmacokinetic profiles.

Lilly noted that patient preference was decided on the patient's evaluation of their experience on the medicine, not on the dosing instructions that accompanied it. Such instructions ensured that patients were aware how to use the medicine in question and could not infer benefits over and above those offered by the product.

As stated in the methods section of the paper, the dosing instructions for sildenafil were based on the manufacturer's instructions. Sildenafil was the only oral PDE5 inhibitor available for the treatment of erectile dysfunction for the 4 years preceding the trial. Indeed in this study, 66% of patients were prior users of sildenafil. In contrast, tadalafil was pre-licence at the time of the study. The tadalafil dosing instructions were derived from instructions used in previous clinical studies and were prototypes for future educational material for patients. The exact dosing instructions used were recorded within the paper. This ensured maximum clarity of the data and allowed readers to make an informed opinion of the potential effect of the differing dosing instructions.

Any potential limitation associated with the use of the different dosing instructions was highlighted in the discussion section, conclusion paragraph of the paper and in both editorials. The authors commented that 'Despite all these limitations, this is one of the first studies to assess preference between oral treatments for ED and to employ a methodology to enhance blinding for ED medications with different dosing instructions'.

Lilly therefore concluded that, while potential bias might exist due to the differences between dosing instructions, this potential was made clear to readers throughout the paper.

Lilly noted that whilst Pfizer acknowledged that von Keitz *et al* included a detailed discussion of the limitations' of the study it was concerned that health professionals might be misled by the abstract at the beginning of the paper. Lilly argued that the paper was available in its entirety precisely to avoid such misinterpretation and to provide maximum transparency of the data as required by Clause 7.2 of the Code. Both editorial comments from Eardley and Montorsi accompanied the paper and went to great lengths to discuss all potential limitations of the study. The discussion and conclusion sections of the paper also detailed the limitations alongside the overall results. Lilly argued that the oversimplified argument proposed by Pfizer underestimated the ability of health professionals to derive informed analytical conclusions from a scientific paper. Again no claims of patient preference appeared on the stand.

Von Keitz *et al* had a number of unique strengths. To reiterate, as stated in the paper, 'Despite these limitations, this is one of the first studies to assess patient preference between PDE5 for ED and the only

study to date to employ a methodology to help ensure blinding for ED medications with different dosing instructions'. The paper was peer reviewed, published in a respected international journal and was available to all health professionals independent of Lilly.

In summary, based on the evidence provided above, Lilly disagreed with the allegation that the use of von Keitz *et al* misled health professionals in breach of Clauses 7.2 and 7.3.

Lilly reassured the Authority that the use of von Keitz *et al* was carefully deliberated and executed to ensure Code compliance and not the alleged breach of undertaking as implied by Pfizer.

Lilly noted that Case AUTH/1578/4/04, referred to a Cialis folder that described two other clinical studies evaluating patient preference (Govier *et al* 2003 and Ströberg *et al* 2003). The Panel ruled that the folder was in breach of the Code as it contained the claims, 'patients prefer Cialis 20mg over sildenafil 50mg' and '90% of men who previously used sildenafil 25-100mg chose to use Cialis (20mg) in the study extension for the treatment of their ED', which were considered unfair. Breaches of Clauses 7.2 and 7.3 were ruled on the claims within the folder, as they were 'not a fair reflection of the data'. As stated in the ruling 'The results had not been presented within the context of the overall limitations of the study'. No ruling referred to the use of the individual papers but rather to claims derived from them. Lilly noted that Case AUTH/1578/4/04 did not pertain to von Keitz *et al*.

Both Govier *et al* and Ströberg *et al* were of different designs to von Keitz *et al*. As the only double-blind, placebo controlled trial offering dose titration, von Keitz *et al* was scientifically more robust than either of the previous studies. Despite this difference and as a result of the previous ruling, Lilly proactively and independently of any direction from the Code, applied some of the learnings from Case AUTH/1578/4/04 to von Keitz *et al*. The paper (when used by itself) was authorised for use only with the inclusion of the two independent editorials, which further reiterated all potential limitations of the study to readers. Furthermore when used proactively by the salesforce, in an effort to ensure the results of the study were always communicated within the setting of the study design, representatives were trained on the use of the clinical paper and provided with a detailed briefing document. This instructed them when discussing the paper with health providers, to always proactively communicate the results of the study alongside its potential limitations. In addition, the briefing document instructed representatives to encourage the doctors to read the whole paper. Lilly reiterated that the stand at the Sexual Dysfunction Association meeting did not bear any claims of patient preference for tadalafil derived from the paper or otherwise, and the clinical paper was not associated with any material that made such claims.

Lilly, therefore refuted the allegation of a breach of Clause 22 by the use of von Keitz *et al* as the undertaking and assurance relating to the Case AUTH/1578/4/04 referred specifically to misleading and unfair claims contained in a folder. Lilly had complied with its undertaking in this regard and had not used the folder since 21 June 2004. As a result, it followed that since there had been no breach of Clause 22, there also had been no breaches of Clauses 9.1 and 2.

Lilly stated that patient preference was increasingly emerging as a scientific endpoint. However the company strongly disagreed that the general consensus was that preference studies provided widely varying results with dubious scientific meaning as submitted by Pfizer. Such a sweeping and unsubstantiated claim undermined rather than progressed scientific research. It was well recognised and substantiated that successful outcome in the treatment of erectile dysfunction was uniquely subjective to the patient (Heaton *et al* 2002). Therefore information on patient preference for one medicine over another was a valuable tool for clinicians. Indeed many highly respected specialists in the field of erectile dysfunction had been involved in the design and/or conduct of PDE5 inhibitor preference studies, either with the industry or independently. Such activity lent further evidence to the interest in scientific answers that could be gained from preference studies.

There were only three peer reviewed, published preference studies available. As with every scientific discipline, learnings from previous studies were addressed in future trial designs. No ideal preference study existed and all had limitations. However, of the published studies available to date, von Keitz *et al* had the most strengths. As yet there was no consensus panel or guidelines regarding preference studies however Mulhall (2004) detailed nine factors, which aimed to minimise bias in such studies. These were listed below; von Keitz *et al* fulfilled the first seven:

1 Properly conducted cross-over study design
2 Randomization of drug sequence
3 Double blinding
4 Inclusion of previous non-responders*
5 Rigorous statistical analysis.
6 Treatment periods of equal length
7 Equivalent drug doses used
8 Balanced dosing instructions
9 Treatment preference assessment after each comparison group period

*All previous sildenafil users were enrolled in the study, irrespective of their response to it. While non-responders were not excluded from enrolment, discrimination between sildenafil responders and non-responders was not recorded.

Lilly therefore concluded that von Keitz *et al* was of scientific merit in the current debate about patient preference for different PDE5 inhibitors. This peer-reviewed paper represented the most up-to-date assessment of patient preference and all results were clearly presented alongside the study limitations. No claims of patient preference for Cialis were associated with the paper or stand.

Lilly referred to the discussions in respect of an alleged breach of Clause 22 above and submitted that it had maintained the high standards and that its actions had not brought discredit upon or reduced confidence in the pharmaceutical industry.

PANEL RULING

The Panel noted that Case AUTH/1578/4/04 concerned a folder entitled Patient Preference Studies issued by Lilly. The claim 'Patients preferred Cialis 20mg over sildenafil 50mg' and '90% of men who had previously used sildenafil 25-100mg chose to use Cialis [20mg] in the study extension for the treatment of their ED' were ruled to be unfair comparisons in breach of Clauses 7.2 and 7.3 of the Code. The relevant studies were Ströberg *et al* and Govier *et al*. The material now at issue was a reprint of another study, von Keitz *et al*, which had been made available from a promotional stand. On balance the Panel considered that the material and circumstances in the case now before it, Case AUTH/1747/7/05, were sufficiently different to those in Case AUTH/1578/4/04 such that there was no breach of undertaking. The Panel thus ruled no breach of Clause 22 of the Code. Consequently no breach of Clause 9.1 and Clause 2 was also ruled.

The Panel noted that von Keitz *et al* had been made available from a promotional stand at a meeting of the Sexual Dysfunction Association. The supplementary information to Clause 11.1 stated that the provision of an unsolicited reprint of an article about a medicine constituted promotion of that medicine and all relevant requirements of the Code must therefore be observed. The Panel noted Lilly's submission that prescribing information had been attached to the paper.

The Panel noted that von Keitz *et al* evaluated patient preference for tadalfil 20mg (Cialis) or sildenafil 50-100mg (Viagra). The two medicines had different dosing instructions in that Cialis could be taken any time between 30 minutes and 24 hours before anticipated sexual activity. Viagra however, had to be taken between 1 and 4 hours before sexual activity. Although very different in that regard von Keitz *et al* nonetheless devised a methodology to help ensure blinding and was unique in that regard. The authors concluded that 73% of patients preferred tadalafil with tadalafil dosing instructions over sildenafil with sildenafil dosing instructions. The study was, however, subject to a number of limitations. The authors themselves stated that had the lower dose of tadalafil (10mg) been used the preference results might have been different.

The Panel noted that although the discussion section of von Keitz *et al* clearly detailed the limitations of the study, and the paper was followed by two critical editorials, the paper nonetheless stated that 73% of patients preferred tadalafil compared with sildenafil. The use of the paper in a promotional context meant that this comparative statement was, in effect, a claim for Cialis v Viagra which was qualified by the small print in the rest of the paper. The editorial by Eardley stated that the defects in the study design limited its applicability to the general population and that further studies with better designs were needed before any firm conclusions could be drawn.

The Panel considered that the use of von Keitz *et al* to promote a patient preference for Cialis v Viagra was misleading. Breaches of Clauses 7.2 and 7.3 were ruled.

Complaint received **27 July 2005**

Case completed **30 September 2005**

CASE AUTH/1748/8/05

NORGINE v SCHWARZ PHARMA

Idrolax leavepiece

Norgine complained about a leavepiece for Idrolax (macrogol 4000) issued by Schwarz Pharma which was intended for use with a range of health professionals in primary and secondary care. Norgine supplied Movicol (macrogol 3350 plus sodium bicarbonate, sodium chloride and potassium chloride).

Page three of the leavepiece headed 'An osmotic laxative without salt', and sub-headed 'Idrolax is the only *salt-free* macrogol laxative', featured three referenced claims, the first read 'Eating too much salt has been linked to higher than average blood pressure, which may lead to an increase in the risk of heart disease and stroke'. Norgine alleged that juxtapositioning this claim with the subheading was a deliberate attempt to disparage Movicol (the only macrogol laxative which contained electrolytes). Norgine alleged that the reference to salt was also disparaging as Movicol did not contain 'salt', it contained Macrogol 3350 plus the electrolytes, sodium, potassium, chloride and bicarbonate specially formulated to minimise electrolyte loss in clinical use.

Norgine noted that one of the references cited was the British Hypertension Society Guidelines and questioned the relevance of these in a leavepiece for a laxative suggesting that they were cited solely to cast doubt in the prescriber's mind about the safety of Movicol. Norgine considered that attempting to link the use of Movicol with an increased risk of hypertension leading to increased risk of heart attack or stroke was extremely irresponsible.

The Panel noted that there were only two macrogol laxatives for the treatment of constipation – Idrolax (macrogol 4000) and Movicol (macrogol 3350 plus electrolytes). The claims that Idrolax was 'An osmotic laxative without salt' and that 'Idrolax is the only *salt-free* macrogol laxative' thus implied that the other macrogol preparation, ie Movicol, was not salt free, which was true. In that regard the Panel considered that Schwarz had not only emphasised the presence of salt in other osmotic laxatives as it had submitted; it had also emphasised the salt content of the only other macrogol laxative.

Immediately after the claims that Idrolax was salt free was the claim that 'Eating too much salt has been linked to higher than average blood pressure which may lead to an increase in the risk of heart disease or stroke'. The Panel accepted that the sodium content of medicines might be important in susceptible individuals but noted that Movicol was not contra-indicated in patients with cardiovascular disease of any kind nor were undesirable cardiovascular effects listed in the Movicol summary of product characteristics (SPC).

The Panel considered that the implied reference to Movicol followed by the statement linking salt ingestion to an increased risk of heart disease and stroke implied that Movicol could cause heart disease and stroke. The Panel considered that the leavepiece was disparaging in this regard and ruled a breach of the Code.

The Panel noted that 'salt' could mean either sodium chloride in particular or an electrolyte in general. The statement from the British Hypertension Society about the eating of too much salt referred specifically to sodium chloride. The claim that Idrolax was the only salt-free macrogol laxative implied that Movicol contained sodium chloride, but only sodium chloride which was not so. The sodium chloride was present as part of a formulation of electrolytes which, according to the Movicol SPC, ensured that there was virtually no net gain or loss in sodium, potassium, or water. The Panel considered that to refer only to 'salt' in this regard was disparaging as alleged and a further breach of the Code was ruled.

The Panel noted that a breach of Clause 2 was a sign of particular censure and reserved for such use. On balance the Panel did not consider that the leavepiece, although disparaging, brought discredit upon or reduced confidence in the pharmaceutical industry.

Norgine Limited complained about a four page leavepiece (ref IDR3057/JAN05) for Idrolax (macrogol 4000) issued by Schwarz Pharma Limited. The piece had been used since January 2005 and was intended for use with general practitioners, district nurses, continence nurse specialists and pharmacists; it had also been used in secondary care. Norgine supplied Movicol (macrogol 3350 plus sodium bicarbonate, sodium chloride and potassium chloride).

COMPLAINT

Norgine noted that page three of the leavepiece was headed 'An osmotic laxative without salt' and sub-headed 'Idrolax is the only *salt-free* macrogol laxative'. The page featured three referenced claims regarding the salt content in the diet and the recommended levels of salt intake. The first of the three claims read 'Eating too much salt has been linked to higher than average blood pressure, which may lead to an increase in the risk of heart disease and stroke'.

Norgine alleged that juxtapositioning the claim that Idrolax was the only 'salt-free' macrogol laxative with the claim about the adverse effects of eating too much salt was a deliberate attempt to disparage Movicol (the only macrogol laxative which contained electrolytes) in breach of Clause 8.1 of the Code. The leavepiece suggested that the 'salt' content of Movicol meant that it was less safe than a 'non-salt' containing laxative (ie Idrolax).

The reference to salt was also alleged to be disparaging in breach of Clause 8.1. Movicol did not contain 'salt', it contained a mixture of Macrogol 3350 plus the electrolytes, sodium, potassium, chloride and bicarbonate specially formulated to minimise electrolyte loss in clinical use. This reference to 'salt' was clearly intended to be derogatory, and disparaged the careful work that went into formulating the product with a balance of electrolytes calculated to

minimise disturbance to serum electrolyte levels in all situations in which the product was used.

Norgine noted that one of the references cited in the leavepiece was the British Hypertension Society Guidelines. The company questioned the relevance of these guidelines in a leavepiece for a laxative and suggested that they were cited solely to cast doubt in the prescriber's mind about the safety of Movicol. Norgine considered that attempting to link the use of Movicol with an increased risk of hypertension leading to increased risk of heart attack or stroke was irresponsible promotion in the extreme. A breach of Clause 2 of the Code was alleged.

RESPONSE

Schwarz noted that the supplementary information to Clause 8.1 of the Code stated that provided that critical references to another company's products were accurate, balanced, fair, etc, and could be substantiated, they were acceptable under the Code.

Schwarz considered that the claims at issue were accurate, balanced and fair. They could be substantiated, as it was a matter of UK governmental policy to encourage a reduction in total salt intake, and Idrolax was the only salt-free macrogol laxative. 'Salt' was both the officially approved and commonly accepted word for sodium chloride. To state that Movicol did not contain 'salt' because it contained sodium chloride in ionic form was disingenuous.

There was no reference in the leavepiece to Movicol, or any means of identifying it in terms of its total salt content. Whilst it was accepted that salt-containing laxatives might have a place in balancing electrolyte loss in induced bowel-clearance, Norgine had provided no evidence to show that there was electrolyte loss in constipation such that compensatory additional electrolyte intake with the laxative was required.

With regard to the heading 'An osmotic laxative without salt' Schwarz noted that Section 1.6.4 of the British National Formulary (BNF) listed the following osmotic laxatives: lactulose, macrogols, magnesium hydroxide, magnesium salts, sodium salts and phosphate enemas. The page heading was accurate, as Idrolax did not contain salts whilst clearly other products within the class did.

With regard to the sub-heading 'Idrolax is the only *salt-free* macrogol laxative' Schwarz noted that each sachet of Movicol contained: macrogol, sodium chloride, sodium bicarbonate and potassium chloride. Sodium chloride was generally referred to as 'salt'; sodium bicarbonate and potassium chloride could all collectively be termed 'salts'. Idrolax did not contain any added salts or electrolytes; therefore Schwarz believed the above statement to be accurate, balanced and fair.

As was stated in the supplementary information to Clause 8.1, much pharmaceutical advertising contained comparisons with other products. In lieu of any clinical trials comparing Idrolax with Movicol, it would seem reasonable to make comparisons based on the content of their summaries of product characteristics (SPCs).

With regard to the claim 'Eating too much salt has been linked to higher than average blood pressure which may lead to an increase in the risk of heart disease and stroke', Schwarz noted that the government, through the Foods Standards Agency and the Scientific Advisory Committee on Nutrition, had recently raised public awareness about the adverse health effects of too much salt. Whilst the issue was of particular concern within certain patient populations, government-funded bodies suggested that the nation as a whole consumed too much salt. The leavepiece outlined the recommended daily amounts, and also the UK average consumption. This information was included to place the issue in context for health professionals, who would then judge whether the salt content of a medicine was a consideration when choosing to prescribe a macrogol for treating constipation. The BNF (Section 1.6.4 on Osmotic Laxatives) specifically suggested that sodium salts should be avoided as they might give rise to sodium and water retention in susceptible individuals.

Schwarz submitted that many publications stated that even small reductions in salt intake could have a significant impact on health. Such reductions might be as small as 1g – the quantity of sodium chloride contained within the maximum dose of Movicol for treating constipation (ie 3 sachets). However, these publications were not cited in the leavepiece so as to avoid references that might be construed as disparaging to Movicol. Similarly, the word safe did not appear in the leavepiece.

Schwarz had deliberately avoided headline references, eg '3g reduction in salt intake in the adult population would lead to a 22% reduction in stroke and a 16% reduction in CHD. This would save 35,000 stroke deaths a year in the UK' (He *et al* 2005).

Schwarz had not named Movicol, nor identified it by listing the actual quantities of the salts that it contained as active ingredients, nor made any specific link between the salt content of other laxatives and disease. Schwarz, therefore, did not consider that the leavepiece was disparaging.

Whilst Schwarz accepted that Norgine was permitted to refer to the salts contained within Movicol as 'electrolytes', Schwarz believed that this term could be potentially misleading; there were many electrolytes, and in Schwarz's experience health professionals were frequently unaware of the sodium chloride content of Movicol. It was specifically sodium chloride that had been linked to increases in blood pressure. Schwarz had, therefore, referred to sodium chloride by its common name, salt. Schwarz maintained that Movicol did contain this substance, as specified in its SPC.

Schwarz noted that Norgine itself referred to the development of Movicol in its promotional literature: 'The concentration of electrolytes in Movicol is calculated....'. This statement cited Fordtran *et al*, (1990) which described gastro-intestinal lavage solutions (Golytely and Golytely-RSS) which were used in gastric lavage, but not in functional constipation. This implied that Movicol was not specifically developed as a treatment for constipation,

but was a reduced dose version of a product licensed for gastric lavage, which might explain its compound formulation.

Schwarz did not refer to the clinical development of Movicol. Whilst these might be interesting points, Schwarz did not believe they were relevant to prescribers, nor to this leavepiece.

Schwarz considered that the British Hypertension Society guidelines were highly relevant when the patient population for laxatives was considered. Approximately 70% of all laxative prescriptions were for patients aged 65 and over. Too much salt could gradually damage the kidneys so they might become less able to excrete excess sodium. This was a particularly important consideration for the over-65 age group. Therefore, the salt content of medicine, as well as a patient's medical history, was an important consideration when deciding which macrogol was most appropriate for an individual.

The number one diagnosis in primary care in the UK was essential (primary) hypertension. Whilst Schwarz did not attempt to dictate to physicians about the management of hypertension, it was clear that a link had been made between the management of hypertension and total dietary salt intake. Schwarz, therefore, considered it responsible and informative to highlight the absence of salt in Idrolax. Schwarz emphasised the presence of salt in other osmotic laxatives, but it was then for the individual prescribers to decide which laxative was most appropriate for their patients.

Schwarz noted that the Movicol SPC contained the following information: 4.4 Special warnings and special precautions for use: 'If patients develop any symptoms indicating shifts of fluid/electrolytes (eg oedema, shortness of breath, increasing fatigue, dehydration, cardiac failure) Movicol should be stopped immediately and electrolytes measured, and any abnormality should be treated appropriately'. No such statement was contained within the Idrolax SPC. Schwarz did not draw attention to this statement in its promotional material, nor did it state that Movicol caused hypertension. Schwarz considered that its leavepiece did not bring discredit to or reduce confidence in the pharmaceutical industry; the leavepiece represented responsible advertising, and discussed issues pertinent to prescribers, particularly for their patients in the over-65 age group who might suffer from multiple pathology, including constipation in the presence of hypertension or renal failure.

PANEL RULING

The Panel noted that there were only two macrogol laxatives for the treatment of constipation – Idrolax (macrogol 4000) and Movicol (macrogol 3350 plus electrolytes). The claims that Idrolax was 'An osmotic laxative without salt' and that 'Idrolax is the only *salt-free* macrogol laxative' thus implied that the other macrogol preparation, ie Movicol, was not salt free, which was true. In that regard the Panel considered that Schwarz had not only emphasised the presence of salt in other osmotic laxatives as it had submitted; it had also emphasised the salt content of the only other macrogol laxative.

Immediately after the claims that Idrolax was salt free was the claim that 'Eating too much salt has been linked to higher than average blood pressure which may lead to an increase in the risk of heart disease or stroke'. The Panel accepted that the sodium content of medicines might be important in susceptible individuals. Section 4.4 of the Movicol SPC, special warnings and special precautions for use, stated that if patients developed any symptoms indicating shifts of fluid/electrolytes (eg oedema, shortness of breath, increasing fatigue, dehydration, cardiac failure) Movicol should be stopped immediately, electrolytes measured and any abnormality treated appropriately. The medicine was, however, not contra-indicated patients with cardiovascular disease of any kind, nor were cardiovascular effects listed in Section 4.8, undesirable effects. Each sachet of Movicol contained 350.7mg sodium chloride. The daily dose of Movicol was 1-3 sachets in divided doses according to response thus the daily dose of sodium chloride derived from the maximum dose of Movicol was 1.05g.

The Panel considered that the implied reference to Movicol followed by the statement linking salt ingestion to an increased risk of heart disease and stroke implied that Movicol could cause heart disease and stroke. The Panel considered that the leavepiece was disparaging in this regard and ruled a breach of Clause 8.1.

The Panel noted that 'salt' could mean either sodium chloride in particular or an electrolyte in general. The statement from the British Hypertension Society about the eating of too much salt referred specifically to sodium chloride. The claim that Idrolax was the only salt-free macrogol laxative implied that Movicol contained sodium chloride, but only sodium chloride which was not so. The sodium chloride was present as part of a formulation of electrolytes which, according to the Movicol SPC, ensured that there was virtually no net gain or loss in sodium, potassium, or water. The Panel considered that to refer only to 'salt' in this regard was disparaging as alleged. A further breach of Clause 8.1 was ruled.

The Panel noted that a breach of Clause 2 was a sign of particular censure and reserved for such use. On balance the Panel did not consider that the leavepiece, although disparaging, brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

Complaint received **1 August 2005**

Case completed **27 September 2005**

CASE AUTH/1749/8/05

CONSULTANT NEUROLOGIST v ALLIANCE

Symmetrel mailing

A consultant neurologist complained about a Symmetrel (amantadine) leaflet issued by Alliance headed 'Are psychotic phenomena in PD [Parkinson's disease] drug related?'. The leaflet subsequently referred to a study which suggested that psychotic phenomena in Parkinson's disease were not drug related (Merims *et al* 2004). The leaflet was signed by a business unit manager and had been sent to neurologists and care of the elderly physicians.

The complainant alleged that the claim was both inaccurate and misleading. Its relationship to the promotion of Symmetrel was unclear. It was inappropriate for a business unit manager to present his view on medical matters which were strictly the province of clinical experts in the field.

The complainant explained that drug-induced psychosis was one of the most common problems encountered in treatment of Parkinson's disease and all specialists responsible for managing the complications of Parkinson's disease recognised the association with medication. If general physicians were given the misleading impression that there was some doubt about whether medicines used for Parkinson's disease could produce hallucinations, this could potentially result in the widespread mishandling of Parkinson's disease medicines.

The Panel noted that the leaflet had been signed by the business unit manager. It was standard practice within the pharmaceutical industry for commercial managers to sign promotional material and so in that regard it did not consider that the leaflet was unacceptable.

The heading 'Are psychotic phenomena in PD drug related' was followed by: 'It is commonly assumed that psychotic phenomena like hallucinations in Parkinson's disease (PD) are drug related. However, it is important to clarify whether this supposition is an accurate one. A recent study used a Cox proportional hazards model to assess the medical records of 422 PD patients – in order to ascertain whether their drug profile was related to the presence of hallucinations'. This statement was referenced to Merims *et al*.

A second heading stated 'No evidence for drug-related hallucinations' beneath which it was explained that Merims *et al* found no correlation between a patient's drug profile and the development of hallucinations. It was stated that daily l-dopa was not significantly different in patients with hallucinations compared with those who had never experienced hallucinations. Age at onset of motor symptoms as well as presence of dementia were identified as definitive risk factors for hallucinations. It was stated that in the light of such clinical data, it would seem reasonable that patients' medical therapy was not delayed, reduced or adjusted.

The Panel noted that the objective of Merims *et al* was to determine the contribution of anti-Parkinson medicines to the development of hallucinations in patients with Parkinson's disease. The authors confirmed that psychotic phenomena were not related simply to drug treatment but that other intrinsic factors might play a role. The Panel considered, however, that the leaflet implied that Parkinson disease medicines had no role in the development of hallucinations. In that regard the Panel noted that hallucinations were listed as an occasional (1-10%) adverse effect of Symmetrel therapy. The Panel considered that the leaflet was misleading in that regard, and a breach of the Code was ruled.

A consultant neurologist complained about a Symmetrel (amantadine) leaflet (ref AL/467/03.05/2.5a) issued by Alliance Pharmaceuticals Ltd. The leaflet was signed by a business unit manager and had been sent to neurologists and care of the elderly physicians.

COMPLAINT

The complainant noted that the leaflet was headed 'Are psychotic phenomena in PD [Parkinson's disease] drug related?'. Beneath the heading was a reference to a study which suggested that psychotic phenomena in Parkinson's disease were not drug related (Merims *et al* 2004).

The complainant alleged that the claim was both inaccurate and misleading. Its relationship to the promotion of Symmetrel was unclear. The complainant considered it inappropriate that a business unit manager had presented his view on medical matters which were strictly the province of clinical experts in the field.

The complainant explained that drug-induced psychosis was one of the commonest problems encountered in treatment of Parkinson's disease and all specialists responsible for managing the complications of Parkinson's disease recognised the association with medication. If general physicians were given the misleading impression that there was some doubt about whether medicines used for Parkinson's disease could produce hallucinations, this could potentially result in the widespread mishandling of anti-Parkinson's disease medicines with consequent avoidable morbidity and indeed mortality in this vulnerable patient group.

It seemed to the complainant inappropriate that such claims were circulated. The evidence in support of the implication that psychotic phenomena were not PD related was insubstantial and irrelevant. It was similar in principle to saying that hypoglycaemic attacks in diabetic patients were not related to insulin use because insulin dose on average was the same in diabetics with hypoglycaemic attacks and those without.

The complainant asked the Authority to ensure that Alliance withdrew the material and circulated a retraction.

When writing to Alliance, the Authority asked it to respond in relation to Clause 7.2 of the Code.

RESPONSE

Alliance stated that the leaflet questioned the widespread belief that psychotic phenomena, including hallucinations, in Parkinson's disease patients were always drug-related by reporting the observations from a retrospective case review (Merims *et al*). The authors compared the profiles of Parkinson's disease patients with hallucinations (n=90) with Parkinson's disease patients without (n=332). A Cox proportional hazards model was used to identify associations between the risk of developing hallucinations and disease variables, such as age at first diagnosis, and l-dopa adjunctive therapies. Hazard ratios were calculated for all these variables.

For l-dopa adjunctive therapies (n=348), including amantadine, hazard ratios were all found to be approximately 1 and were not statistically significant ($p>0.05$). Merims *et al* therefore concluded that none of the agents commonly used as adjuncts to l-dopa constituted a risk for developing hallucinations.

When hazard ratios were calculated for the presence of dementia and the age of onset of motor symptoms, they were found to be significantly related to the risk of developing hallucinations. 'Are psychotic phenomena in PD drug related?' was not a claim but a question. Furthermore, it was neither inaccurate nor misleading based on the observations of Merims *et al*.

Merims *et al* examined the risk of developing hallucinations following treatment with a number of anti-Parkinson's disease medications, including amantadine and found that amantadine as an adjunct to l-dopa was not a risk factor for developing hallucinations (hazard ratio 1.06, $p=0.792$). In their conclusions, the researchers did not differentiate between the various adjunctive therapies reviewed but stated that 'Supplementary treatment with amantadine, selegiline, dopamine agonists, entacapone and anticholinergics did not increase the risk for the development of hallucinations'. In not referring specifically to amantadine but Parkinson's disease medicines in general, the leaflet did not overstate the benefits of amantadine.

As amantadine was widely used in Parkinson's disease with a well established safety profile that included the risk of psychotic events and hallucinations, it was appropriate to refer to this study in the promotion of Symmetrel. The leaflet was clearly branded as a Symmetrel promotional item and included the prescribing information that referred to both psychosis and hallucinations. The leaflet did not report the personal views of the business unit manager on medical matters. Rather it presented the observations of a group of independent researchers that were published in a peer reviewed, clinical journal.

Merims *et al* questioned the widespread belief that psychotic phenomena in Parkinson's disease patients were generally medicine related. The etiology of psychotic phenomena in Parkinson's disease was complex and they might arise as a natural consequence of the disease. Draft clinical guidelines on the management of Parkinson's disease recommended that when psychosis developed, its initial treatment should include a general medical assessment and consideration that medicine which might have triggered the psychotic episodes be withdrawn (Section 9.42. Parkinson's disease, Diagnosis and Management in Primary and Secondary Care. Draft for first consultation. NICE August 2005).

There was no doubt that Parkinson's disease medicines could cause hallucinations, this was a recognised adverse effect and was listed in the summaries of product characteristics (SPCs) for several agents including Symmetrel. What Merims *et al* and the draft NICE guidelines highlighted was that the development of psychosis should not automatically be assumed to be an adverse effect of therapy. Questioning the link between a patient's medicine and hallucinations was not misleading and might result in the more effective use of Parkinson's disease medicines.

Merims *et al* was published in the Journal of Neural Transmission, which was not normally seen by the majority of clinicians who treated Parkinson's disease in the UK. It was therefore appropriate to bring this study to their attention.

Merims *et al* reported a retrospective case review. Whilst such a study design was not at the top of the hierarchy of clinical evidence, the paper clearly described the methodology and the statistical methods. The conclusions of such a study were not definitive but were indicative. In their introduction, Merims *et al* reviewed previous work which also suggested that psychotic phenomena in Parkinson's disease and Parkinson's disease medicines were not necessarily directly linked. The authors further referred to an unpublished study which suggested that there might be a genetic factor. This evidence, whilst limited, legitimately questioned the link between the development of hallucinations and Parkinson's disease medicine, it was therefore relevant. Alliance currently had no plans to reuse this piece which had been used to highlight a recent clinical paper that was likely to have been missed by most clinicians. Alliance did not consider it appropriate to issue a retraction as it would imply that the company no longer accepted the observations of an independent research group.

PANEL RULING

The Panel noted the complainant's comments regarding the leaflet being signed by the business unit manager. In the Panel's view it was standard practice within the pharmaceutical industry for commercial managers to 'sign' promotional material and so in that regard it did not consider that the leaflet was unacceptable. Readers of material signed by a commercial manager would know, at the outset, that the material they were reading was promotional.

The heading of the leaflet 'Are psychotic phenomena in PD drug related' was followed by: 'It is commonly assumed that psychotic phenomena like hallucinations in Parkinson's disease (PD) are drug related. However, it is important to clarify whether this supposition is an accurate one. A recent study used a Cox proportional hazards model to assess the medical records of 422 PD patients – in order to

ascertain whether their drug profile was related to the presence of hallucinations'. This statement was referenced to Merims *et al*.

A second heading stated 'No evidence for drug-related hallucinations' beneath which it was explained that Merims *et al* found no correlation between a patient's drug profile and the development of hallucinations. It was stated that daily l-dopa was not significantly different in patients with hallucinations compared with those who had never experienced hallucinations. Age at onset of motor symptoms as well as presence of dementia were identified as definitive risk factors for hallucinations. It was stated that in the light of such clinical data, it would seem reasonable that patients' medical therapy was not delayed, reduced or adjusted.

The Panel noted that the objective of Merims *et al* was to determine the contribution of anti-Parkinson medicines to the development of hallucinations in patients with Parkinson's disease. The authors confirmed that psychotic phenomena were not related simply to drug treatment but that other intrinsic factors might play a role.

The Panel considered, however, that the leaflet implied that Parkinson's disease medicines had no role in the development of hallucinations. In that regard the Panel noted that hallucinations were listed as an occasional (1-10%) adverse effect of Symmetrel therapy. The Panel considered that the leaflet was misleading in that regard. A breach of Clause 7.2 was ruled.

The Panel noted the complainant's request that Alliance be made to issue a retraction, or corrective statement. Only the ABPI Board of Management had the power to compel companies to issue corrective statements. The first step that the Panel would have to take towards this would be to report Alliance to the Code of Practice Appeal Board. Such a sanction was only exercised for, *inter alia*, serious breaches of the Code. The Panel did not consider the matter before it warranted such action. The Appeal Board could decide to report the matter to the ABPI Board of Management regardless of whether or not the Panel made a formal report to it.

Complaint received **3 August 2005**

Case completed **20 September 2005**

JOHNSON & JOHNSON WOUND MANAGEMENT v BAXTER HEALTHCARE

Promotion of Tisseel

Johnson & Johnson Wound Management alleged that Baxter Healthcare had promoted Tisseel Fibrin Sealant Kit in a manner which was inconsistent with the particulars listed in the summary of product characteristics (SPC). The SPC stated 'Tisseel is intended to complement good surgical technique in achieving haemostasis, or obtaining a watertight seal of the dura mater'. Johnson & Johnson Wound Management noted that the first sentence of the indication appeared to refer to haemostasis and sealing of the dura mater only ie during neurosurgical procedures. However Baxter Healthcare had interpreted the comma after haemostasis to mean that Tisseel could be used to complement good surgical technique in achieving haemostasis in surgery in general. Johnson & Johnson Wound Management would have expected a full stop after the word 'haemostasis' if this were the case.

The Panel noted the sentence at issue in the Tisseel SPC and considered that it could be interpreted either to mean that Tisseel was indicated for haemostasis generally or that it was only so indicated in relation to obtaining a watertight seal of the dura mater. The promotional material provided by Baxter Healthcare discussed the use of Tisseel in neurosurgery, cardiovascular surgery fibrin sealants, the Tisseel kit and preparation of the sealant. The Panel did not consider that the material provided was inconsistent with the SPC as alleged. No breach of the Code was ruled.

Johnson & Johnson Wound Management complained about the promotion of Tisseel Fibrin Sealant Kit by Baxter Healthcare Ltd. The Tisseel promotional material provided by Baxter Healthcare comprised a product monograph (ADV:05/191B) four brochures (ADV: 1696 B, ADV 05/189B, ADV 05/192B, ADV 05/001 B), a poster (ADV 05/179B), an Easy prep reconstitution guide (ADV 05/101B), a flyer (ADV 05/194B) and an example invitation letter to a Baxter Healthcare BioSurgery day (ADV 05/881B).

Inter-company correspondence had failed to resolve the matter.

COMPLAINT

Johnson & Johnson Wound Management alleged that Tisseel was currently being promoted in a large number of departmental areas, including burns and plastic surgery.

Johnson & Johnson Wound Management noted Clause 3.2 of the Code which stated that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics (SPC). Johnson & Johnson Wound Management alleged that Baxter Healthcare was incorrectly interpreting the indication in its current SPC. The authorized indication was as follows:

> 'Tisseel is intended to complement good surgical technique in achieving haemostasis, or obtaining a watertight seal of the dura mater. Tisseel Kit is used as an adjunct to haemostasis in cardiopulmonary bypass surgery when control of bleeding by conventional surgical techniques including, sutures, ligatures, and cautery is considered ineffective or impractical. Tisseel Kit is used as an adjunct to dura sealing when control of cerebrospinal fluid (CSF) leakage by conventional neurosurgical techniques including sutures and patches is considered insufficient or impractical.'

Johnson & Johnson Wound Management noted that the first sentences of the indication appeared to refer to haemostasis and sealing of the dura mater only (ie during neurosurgical procedures). However, the placement of the comma after the word 'haemostasis' had been interpreted by Baxter Healthcare to be a stand-alone statement, ie that Tisseel was intending to complement good surgical technique in achieving haemostasis in surgery in general. Johnson & Johnson Wound Management would have expected a full stop after the word 'haemostasis' if this were the case.

Johnson & Johnson Wound Management noted that under the European Medicines Evaluation Agency (EMEA) Core SPC for Plasma Derived Fibrin Sealant/ Haemostatis Products (CPMP/BPWG/153/00), fibrin sealants for which appropriate safety and efficacy data were available might be approved for a general indication for use as an adjunct to haemostasis in surgery. However, the SPC for Tisseel pre-dated the adoption of this guideline and was not consistent in other areas with the wording of this core SPC. Thus, Johnson & Johnson Wound Management alleged that Baxter Healthcare was promoting Tisseel in a manner consistent with the new Core SPC without applying for, nor being granted, a variation to the Tisseel marketing authorization.

Johnson & Johnson Wound Management stated that it had requested supporting evidence that the broad interpretation of the approved indication was indeed correct and, as of this date, it had received no written data of explanation. The original query in May 2005 was to the Business Unit Manager of Baxter Healthcare Biosurgical Division. This was followed up twice in June and once in July. Johnson & Johnson Wound Management had, however, been verbally informed by Baxter Healthcare that it intended to continue promoting Tisseel as an adjunct to haemostasis in all surgical specialties.

Johnson & Johnson Wound Management sought evidence in writing from Baxter Healthcare as to whether the Medicines Healthcare products Regulatory Agency (MHRA) intended that the wording of the

indication should be interpreted to include use as an adjunct to haemostasis in surgery in general.

Johnson & Johnson Wound Management considered that clarification of the correct interpretation of the approved indication for Tisseel would be of benefit to all parties.

RESPONSE

Baxter Healthcare noted that Johnson & Johnson Wound Management had correctly quoted the current licensed indication for Tisseel but Baxter Healthcare refuted the alleged breach of Clause 3.2 and submitted that it was promoting the use of Tisseel in an appropriate manner and in accordance with the marketing authorization.

Baxter Healthcare acknowledged that when Tisseel was originally licensed in the UK its indication was limited to haemostasis in cardiopulmonary bypass surgery only and it submitted that its promotional material reflected this limitation. In December 2003 the Tisseel indication was broadened following a thorough review by the Committee on Safety of Medicines. This resulted in the addition of the first sentence of the current licence;

'Tisseel is intended to complement good surgical technique in achieving haemostasis, or obtaining a watertight seal of the dura mater' and also the specific neurosurgical indication;

'Tisseel kit is used as an adjunct to dural sealing when control of cerebrospinal fluid leakage by conventional neurosurgical techniques including sutures and patches is considered insufficient or impractical'.

Baxter Healthcare acknowledged that Johnson & Johnson had requested evidence from it, in writing, of the MHRA's intention as to the interpretation of the Tisseel approved indication. Baxter Healthcare submitted that the 'intent' of the MHRA was reflected in the wording of the licensed indication that was granted and thus it considered that it had promoted the product in accordance with the current marketing authorization.

PANEL RULING

The Panel noted that according to Section 4.1 of its SPC dated January 2005 the therapeutic indications were that Tisseel was intended, *inter alia*, to 'complement good surgical technique in achieving haemostasis, or obtaining a watertight seal of the dura mater'. The Panel considered that the punctuation was such that this could be interpreted in one of two ways; either Tisseel was indicated for haemostasis generally, or it was only so indicated in relation to obtaining a watertight seal of the dura mater. The following paragraph of the SPC gave details about the use of Tisseel in cardiopulmonary surgery and as an adjunct to dura sealing. The Panel noted the submissions of the parties.

The promotional material provided by Baxter Healthcare discussed the use of Tisseel in neurosurgery, cardiovascular surgery fibrin sealants, the Tisseel kit and preparation of the sealant. The Panel did not consider that the material provided was inconsistent with the SPC as alleged. No breach of Clause 3.2 was ruled.

Complaint received **15 August 2005**

Case completed **11 October 2005**

CASE AUTH/1754/9/05

ANONYMOUS MEDICAL REPRESENTATIVE v MERCK

Briefing material for Niaspan

An anonymous representative from Merck alleged that briefing material for Niaspan (prolonged release nicotinic acid) asked representatives to promote a starting dose which was inconsistent with that stated in the summary of product characteristics (SPC). The SPC gave a titration schedule of 375mg once daily in week one, 500mg once daily in week two, 750mg once daily in week three and 1000mg once daily in weeks four to seven. Thereafter the once daily dose could be increased to 1500mg and again to 2000mg depending on patient response and tolerance.

The Panel noted that a senior regional business manager's email stated that the 750mg dose of Nisapan was 'too much too soon for some' and referred to the most common way of initiating Nisapan in the US which was to use '1 x 500mg tablet for the first month (at night) and then double the dose thereafter ie use 2 x 500mg tablets at night. Fewer patients complain of flushing during this regimen'.

The email further stated that 'Marketing are keen for us to incorporate this into our detail when closing etc (they hope to make changes to materials in due course) – you can say that there is a starter pack available, however, most people are adopting the way in which Niaspan is used in the States the simplest and most convenient way for doctors to prescribe and for patients to take the medication – without causing undue side effects that is one 500mg tablet taken last thing at night for the first month and then x 2 500mg tablets thereafter etc or words to taht [sic] effect'.

The Panel considered that the email constituted briefing material about how to promote Niaspan. It did not accept Merck's submission that the promotion of the US dose depended on further briefing of the representatives by the senior regional business manager and further information for the representatives that had not yet been provided. In the Panel's view a representative receiving the email was being instructed to promote the US dosing schedule forthwith when closing a meeting. A suggested script was provided.

The Panel considered that the email was inconsistent with the UK SPC for Niaspan and advocated a course of action likely to lead to a breach of the Code. The Panel therefore ruled breaches of the Code.

COMPLAINT

An anonymous medical representative from Merck Pharmaceuticals UK alleged that he was being asked to promote Niaspan prolonged release nicotinic acid out of its licensed indication. From the memorandum provided it could be seen that he was being asked to promote a 500mg starting dose in place of the starter pack.

When writing to Merck, the Authority asked it to respond in relation to Clauses 3.2 and 15.9 of the Code.

RESPONSE

Merck stated that the author of the memorandum (an email) was a senior regional business manager. The 'team' referred to in the greeting 'Dear Team' was the regional team, not the national sales team. Those sent the email were the sales team for the region. No head office staff were copied in to the email and the senior regional business manager was acting upon his own initiative and not following instruction from head office.

Merck knew that the US practice for titrating Niaspan differed from the UK summary of product characteristics (SPC) and had heard that this practice reduced the side effect of flushing. The US titration schedule was raised as an issue by Merck's field trainer in October 2004, so clearly this matter had become widely known within the company by this time. Email correspondence from the time showed that the medical department made it clear that the SPC prevented Merck from promoting this alternative regimen. The medical department however agreed to look into the matter, collect data from the company which marketed Niaspan in the US and consider what, if anything, could be briefed to the sales force.

In the end, the only approved briefing given to the representatives on this matter was contained in a Q&A document on Niaspan under the heading of 'Dosage and Administration'. It read: Q 'Can I titrate more slowly than the recommended titration schedule?' – A 'Please ask the medical information dept for this information, for you to give to your customer'.

The senior regional business manager's email to his sales force advocated the promotion of the US titration regime. It stated that this would be discussed in one to one meetings and that there was a hope of promotional materials to support this message. The email was sent late one Monday morning. Two days later one of the representatives in the region emailed the medical information department asking for more information which would enable them to promote this dosing schedule, forwarding the senior business manager's email by way of explanation for the request. The head of medical information alerted head office staff to the senior regional business manager's email as soon as she opened the email at the start of Friday morning. Her response made clear that the senior regional business manager's email was unacceptable. The senior regional business manager's manager telephoned him the same day, the position of the company was made clear and any plans to promote this dose schedule were halted.

This course of events ensured that any plans to promote this schedule were prevented. Promotion depended upon further briefing of the representatives

by the senior regional business manager and further information to the representatives (as requested from medical information) which was not forthcoming. The whole idea was halted within a week. Merck was confident, therefore, that a breach of Clause 3.2 was prevented.

The email from the senior regional business manager constituted a briefing to representatives advocating a dosing regime that was not in line with the product licence. Merck contended that, on its own, it was insufficient to actually cause a breach of Clause 3.2 and, therefore, was technically not a breach of Clause 15.9.

Merck was uncertain why this had been raised as a complaint and if the complainant was a representative as this was not a current issue.

In summary, this email was sent on the initiative of a regional manager, against company policy. Merck acted swiftly and appropriately to this matter, ensuring that any beach of the Code was prevented.

PANEL RULING

The Panel noted that the senior regional business manager's email stated that the 750mg dose of Nisapan was 'too much too soon for some' and referred to the US situation and the most common way of initiating Nisapan in the US was to use '1 x 500mg tablet for the first month (at night) and then double the dose thereafter ie use 2 x 500mg tablets at night. Fewer patients complain of flushing during this regimen'.

The email further stated that 'Marketing are keen for us to incorporate this into our detail when closing etc (they hope to make changes to materials in due course) – you can say that there is a starter pack available, however, most people are adopting the way in which Niaspan is used in the States the simplest and most convenient way for doctors to prescribe and for patients to take the medication – without causing undue side effects that is one 500mg tablet taken last thing at night for the first month and then x 2 500mg tablets thereafter etc or words to taht [sic] effect'.

The Panel considered that the email constituted briefing material about how to promote Niaspan. It did not accept Merck's submission that the promotion of the US dose depended on further briefing of the representatives by the senior regional business manager and further information for the representatives that had not yet been provided. In the Panel's view a representative receiving the email was being instructed to promote the US dosing schedule forthwith when closing a meeting. A suggested script was provided.

The Niaspan SPC gave a titration schedule of 375mg once daily for week 1, 500mg once daily for week 2, 750mg once daily for week 3, and 1000mg once daily for weeks 4-7. Thereafter the once daily dose could be increased to 1500mg and again to 2000mg depending upon patient response and tolerance.

The Panel noted that the US titration schedule referred to in the email was different to that of the UK. The email was thus inconsistent with the UK SPC and advocated a course of action likely to lead to a breach of the Code. The Panel therefore ruled breaches of Clauses 3.2 and 15.9.

Complaint received **2 September 2005**

Case completed **29 September 2005**

PRIMARY CARE TRUST MEDICAL DIRECTOR v MERCK SHARP & DOHME

Conduct of representative

A medical director at a primary care trust (PCT) complained that the conduct of a representative from Thomas Morson Pharmaceuticals, a Division of Merck Sharp & Dohme, was such that it would damage the reputation of the company.

The complainant explained that whilst the representative had been waiting to make an appointment with a general practitioner (GP), a 14 year old girl came in with her parents and went in to see the GP. The representative was then told to come back later to see the GP and he left the building. The girl and her parents then came out of the consulting room and also left the building. Very shortly afterwards they came back bearing the representative's business card which he had left on the windscreen of the patient's parents' car in the surgery car park. The representative had left the car park by this time. The back of the business card bore the handwritten message: 'Would love to take you out for a drink sometime! Call me if interested! [representative's initials]'. The girl's father was obviously extremely angry.

Subsequently the PCT manager ascertained from the representative that the invitation on the card was directed towards the daughter, not the mother. The representative was apparently shocked to be told that the girl was only 14 years old, stating that she looked older. He apologised and said that he had been 'stupid'.

The PCT viewed the representative's conduct as grossly unprofessional.

The Panel considered that what had happened was within the scope of the representative's employment because the meeting with the girl, such as it was, had occurred in a general practice surgery where the representative had been present in a business capacity. Furthermore the note had been written on a business card and left while the car was in the surgery car park. What had happened was quite unacceptable and the Panel ruled breaches of the Code including a breach of Clause 2.

COMPLAINT

A medical director at a local teaching primary care trust (PCT) stated that he had serious concerns about the professional conduct of a representative, from Thomas Morson Pharmaceuticals, a Division of Merck Sharp & Dohme.

The representative had been waiting to make an appointment with a general practitioner (GP). A 14 year old girl came in with her parents and went in to see the GP. The representative was then told he would have to come back later to see the GP and left the building. The girl and her parents then came out of the consulting room and also left the building. Very shortly afterwards they came back bearing the representative's business card which he had left on the windscreen of the patient's parents' car in the surgery car park. The representative had left the car park by this time. The back of the business card bore the handwritten message: 'Would love to take you out for a drink sometime! Call me if interested! [representative's initials]'. The girl's father was obviously extremely angry. A PCT manager who was present at the time managed to calm him down and said that she would contact the representative. The family then left.

Subsequently the PCT manager called the representative on his mobile telephone and described what had happened. She asked him to clarify whether the invitation on the card was intended for the mother or the daughter. The representative replied that it was directed towards the daughter. He was apparently shocked to be told that she was only 14 years old, stating that she looked older. He apologised and said that he had been 'stupid'.

The PCT viewed the representative's conduct as grossly unprofessional. The complainant assumed that it would also be regarded as damaging to the reputation of the company.

The representative's comments on his perception of the girl's age did not, in the PCT's view, in any way lessen the serious nature of his behaviour. The PCT was naturally concerned that this behaviour might recur, potentially with more serious outcomes, or that this might not be the first time he had exhibited such behaviour.

When writing to Merck Sharp & Dohme the Authority asked it to respond in relation to Clauses 2 and 15.2 of the Code.

RESPONSE

Merck Sharp & Dohme stated that it had been able to verify the representative's account with the visiting PCT practice manager who was at the surgery on the day.

The representative admitted that he left his business card on the car windscreen and that the invitation was intended for the daughter. He was contacted by the patient's mother later that morning and it was only at this point that he became aware of the girl's age. He had thought that she looked significantly older. He apologised profusely to the mother and he also spoke to the father and again apologised. At the end of that brief conversation the representative believed that his unreserved apology had been accepted and that the matter was closed.

The representative then returned to the surgery and spoke to the practice manager. He said that he had 'done something very silly' and apologised for his actions. He informed the practice manager of the conversation with the parents as described above.

The practice manager then rang the father and the above account was verified by him and he confirmed that he viewed the matter as closed.

When Merck Sharp & Dohme investigated this matter the representative stated that leaving the business card on the car was a 'spur of the moment' action which he had never done before. He accepted that his actions were a profound error of judgement which he deeply regretted and was extremely embarrassed by.

The representative returned that afternoon to fulfil his appointment and saw the GP as planned. He believed that a line had been drawn under the incident as his apology had been accepted by both the patient's parents and the surgery.

Merck Sharp & Dohme accepted that the representative had committed a very serious error of judgement and it would take appropriate disciplinary action. The company was committed to ensuring that its representatives upheld the highest standards of behaviour in the discharge of their duties.

Merck Sharp & Dohme would write to the PCT with the results of its investigation with outcomes which it believed addressed the complainant's wider concerns. Merck Sharp & Dohme also apologised unreservedly to the patient and her parents for any distress which its representative's actions might have caused them.

PANEL RULING

The Panel noted Clause 15.10 of the Code which stated: 'Companies are responsible for the activities of their representatives if these are within the scope of their employment even if they are acting contrary to the instructions which they have been given'.

It was sometimes difficult to know where a line had to be drawn as to what was, or was not, within the scope of employment. In the present case the Panel considered that what had happened was within the scope of the representative's employment because the meeting with the girl, such as it was, had occurred in a general practice surgery where the representative had been present in a business capacity. Furthermore the note had been written on a business card and left while the car was in the surgery car park.

What had happened was quite unacceptable and the Panel ruled breaches of Clauses 2 and 15.2 of the Code.

Complaint received **5 September 2005**

Case completed **4 October 2005**

CASES AUTH/1756/9/05

PRINCIPAL PHARMACIST and MEDICINES INFORMATION MANAGER v SERVIER

Coversyl journal advertisement

A hospital principal pharmacist and a medicines information manager jointly alleged that the claim 'The preliminary results of ASCOT, in addition to EUROPA and PROGRESS, prove that BP lowering with COVERSYL [perindopril] 4-8mg can reduce the risk of a CV event' was misleading. The claim had appeared in a journal advertisement issued by Servier. The complainants stated that it was clear from the results of the PROGRESS study that Coversyl monotherapy did not reduce the incidence or risk of a cardiovascular event.

The Panel noted that the claim at issue was preceded by the statement 'ASCOT is the latest of 3 eminent trials to demonstrate the benefits of COVERSYL for patients with hypertension'. The Panel thus did not accept Servier's submission that the claim at issue clearly conveyed the message that it was a combination of the results from all three studies that proved an effect; the preceding statement implied that each study showed a benefit for Coversyl. With regard to PROGRESS this was not so. The Panel considered that the claim was misleading as alleged. A breach of the Code was ruled.

A hospital principal pharmacist, and a medicines information manager jointly complained about a journal advertisement (ref 05COAD424) for Coversyl (perindopril) issued by Servier Laboratories Ltd.

COMPLAINT

The complainants alleged that the prominent claim that 'The preliminary results of ASCOT, in addition to EUROPA and PROGRESS, prove that BP lowering with COVERSYL 4-8mg can reduce the risk of a CV event' was misleading.

The complainants stated that from the results of PROGRESS it was clear that Coversyl did not reduce the incidence or risk of a CV event. Indeed the authors of the study stated 'Among participants treated with perindopril alone … stroke risk was not discernibly different from that among participants who received placebo alone'.

The PROGRESS study included a patient group who received a ***combination*** of perindopril and a diuretic and there was a significant reduction in stroke incidence compared with placebo. However, since there was no arm of the study in which patients received a diuretic alone, it was not possible to know if it was the diuretic or the drug combination which was responsible for the apparent therapeutic benefit.

When writing to Servier, the Authority asked it to respond in relation to Clause 7.2.

RESPONSE

Servier considered that the claim at issue clearly conveyed the message that the preliminary results of ASCOT, **in addition** to EUROPA and PROGRESS, proved an effect that Coversyl had ie a combination of the results from all three studies proved an effect of Coversyl. From the wording of this claim Servier did not consider it reasonable that any one of the studies was singled out solely to support the 'effect' that Servier was claiming that Coversyl had.

Servier considered that the first paragraph in the advertisement added emphasis to the 'effect' that the company claimed Coversyl had. 'ASCOT is the latest of 3 eminent trials to demonstrate the benefits of COVERSYL for patients with hypertension'.

The 'effect' that the ASCOT, EUROPA and PROGRESS studies proved was that Coversyl lowered blood pressure and by lowering blood pressure could reduce the risk of a cardiovascular event. It was widely accepted in medical practice that blood pressure reduction in hypertensive patients was fundamental for the prevention of cardiovascular events. Verdecchia *et al* (2005) analysed the extracted summary statistics of 28 cardiovascular outcome trials (including PROGRESS and EUROPA) and concluded that '… BP lowering is fundamental for prevention of CHD and stroke'. The editorial commentary on this publication (Kaplan 2005) confirmed this statement 'As this analysis shows again, the lower the blood pressure as provided by any drug, the greater the protection against CHD and stroke'.

ASCOT, PROGRESS and EUROPA all demonstrated that Coversyl alone or in combination effectively reduced blood pressure in hypertensive patients (in accordance with Coversyl's licensed indication). As it was widely accepted in medical practice that lowering blood pressure reduced the risk of a CV event, Servier submitted that the claim 'The preliminary results of ASCOT, in addition to EUROPA and PROGRESS, prove that BP lowering with COVERSYL 4-8mg can reduce the risk of a CV event' was not misleading as alleged. The company denied a breach of the Code.

PANEL RULING

The Panel noted that beneath the heading 'Coversyl can …' the advertisement read 'ASCOT is the latest of 3 eminent trials to demonstrate the benefits of COVERSYL for patients with hypertension'. The second paragraph featured the claim at issue and read 'The preliminary results of ASCOT, in addition to EUROPA and PROGRESS, prove that BP lowering with Coversyl 4-8mg can reduce the risk of a CV event'. The Panel did not accept Servier's submission that the claim at issue clearly conveyed the message that it was a combination of the results from all three studies that proved an effect. The first paragraph implied that each study showed a distinct benefit for

Coversyl. The Panel considered that the claim at issue would be read by the majority as implying that the ASCOT data added to a pre-existing body of data (EUROPA and PROGRESS) which showed that blood pressure lowering with Coversyl 4-8mg could reduce the risk of a CV event. There was no implication that it was the combined effect of such data that reduced the risk of a CV event.

The Panel noted the PROGRESS study was designed to determine the effects of a blood pressure lowering regimen in hypertensive and non-hypertensive patients with a history of stroke or transient ischaemic attack. Active treatment comprised a flexible regimen based on perindopril (4mg daily) with the addition of indapamide (2.5mg daily). No data was obtained for indapamide alone. The findings section stated that combination therapy reduced blood pressure by 12/5mm Hg and stroke risk by 43%. Monotherapy reduced blood pressure by 5/3mm Hg and produced no discernable reduction in the risk of stroke.

The Panel considered that the advertisement implied that all three studies, ASCOT, EUROPA and PROGRESS proved that blood pressure lowering with Coversyl (alone) could reduce the risk of a CV event. With regard to PROGRESS, this was not so. There was no allegation about the ASCOT and EUROPA studies.

The claim was misleading as alleged and a breach of Clause 7.2 of the Code was ruled.

Complaint received **5 September 2005**

Case completed **14 October 2005**

CODE OF PRACTICE REVIEW – NOVEMBER 2005

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

1603/7/04	**Aventis Pharma v Novo Nordisk**	**Hospitality at meetings**	**Two breaches Clause 19.1** **Audit required by Appeal Board** **Follow-up audit required by Appeal Board**	**Report from Panel to Appeal Board**	**Page 3**
1697/3/05	**GlaxoSmithKline v Takeda**	**Promotion of Actos**	**Breach Clause 7.2**	**Appeal by respondent**	**Page 8**
1703/4/05	General Practitioner v Takeda	Market research questionnaire	No breach	No appeal	Page 13
1714/5/05	**Anonymous Employee v AstraZeneca**	**Call rates**	**Breaches Clauses 9.1 and 15.4**	**No appeal**	**Page 16**
1715/6/05	**Hospital Consultant v Cephalon**	**Actiq presentation**	**Breaches Clauses 3.2 and 15.2**	**No appeal**	**Page 20**
1718/6/05 and 1719/6/05	General Practitioner v Reckitt Benckiser Healthcare and Britannia	Promotion of Gaviscon Advance	No breach	No appeal	Page 22
1720/6/05 and 1721/6/05 and 1722/6/05	**General Practitioners v Astellas**	**Regional advisory board meetings**	**Breaches Clauses 9.1 and 18.1**	**No appeal**	**Page 25**
1723/6/05 and 1724/6/05	**Primary Care Trust Clinical Pharmacists v Reckitt Benckiser Healthcare and Britannia**	**Promotion of Gaviscon Advance**	**Breaches Clauses 7.2 and 15.2**	**No appeal**	**Page 29**
1727/6/05 and 1732/6/05	**Primary Care Trust Chief Pharmacist and Head of Medicines Management v Ranbaxy**	**Mirtazapine letter**	**Breaches Clauses 7.2, 9.1 and 17.1**	**No appeal**	**Page 31**
1730/6/05	**Takeda/Director v GlaxoSmithKline**	**Promotion of Avandamet**	**Three breaches Clause 7.2** **Three breaches Clause 7.4**	**No appeal**	**Page 33**
1733/7/05	General Practitioner v Dermal Laboratories	Unsolicited mail	No breach	No appeal	Page 44
1734/7/05	Anonymous v Bristol-Myers Squibb	Taxol support kits	No breach	No appeal	Page 45
1735/7/05	**Novo Nordisk v Sanofi-Aventis**	**Letter to health professionals**	**Breaches Clauses 4.1, 4.3, 7.4 and 8.1** **Two breaches Clause 7.2**	**No appeal**	**Page 47**
1736/7/05	**Roche v Abbott**	**Reductil leavepiece**	**Breaches Clauses 3.2, 7.2, 7.3 and 7.10**	**No appeal**	**Page 49**

1739/7/05	**General Practitioner v Novartis**	**Stepwise campaign**	**Breach Clause 20.2**	**No appeal**	**Page 55**
1740/7/05	Sankyo Pharma v Boehringer Ingelheim	Micardis leavpiece	No breach	No appeal	Page 57
1741/7/05	**Local Health Board Prescribing Advisor v Bayer**	**Arrangements for a meeting**	**Breaches Clauses 2, 9.1, 15.2 and 19.1**	**No appeal**	**Page 60**
1742/7/05	**Primary Care Trust Head of Medicines Management v Merck**	**Conduct of representative**	**Breaches Clauses 2, 9.1, 15.2 and 18.1**	**No appeal**	**Page 62**
1744/7/05	**Hospital Lead Pharmacy Technician v AstraZeneca**	**Conduct of representative**	**Breach Clause 15.4**	**No appeal**	**Page 64**
1746/7/05	**Local Health Board Prescribing Adviser v Trinity-Chiesi**	**Conduct of representatives**	**Breaches Clauses 7.2 and 15.2**	**No appeal**	**Page 66**
1747/7/05	**Pfizer/Director v Lilly**	**Use of clinical paper to promote Cialis**	**Breaches Clauses 7.2 and 7.3**	**No appeal**	**Page 68**
1748/8/05	**Norgine v Schwarz Pharma**	**Idrolax leavepiece**	**Two breaches Clause 8.1**	**No appeal**	**Page 73**
1749/8/05	**Consultant Neurologist v Alliance**	**Symmetrel mailing**	**Breach Clause 7.2**	**No appeal**	**Page 76**
1751/8/05	Johnson & Johnson Wound Management v Baxter Healthcare	Promotion of Tisseel	No breach	No appeal	Page 79
1754/9/05	**Anonymous Medical Representative v Merck**	**Briefing material for Niaspan**	**Breaches Clauses 3.2 and 15.9**	**No appeal**	**Page 81**
1755/9/05	**Primary Care Trust Medical Director v Merck Sharp & Dohme**	**Conduct of representative**	**Breaches Clauses 2 and 15.2**	**No appeal**	**Page 83**
1756/9/05	**Principal Pharmacist and Medicines Information Manager v Servier**	**Coversyl journal advertisement**	**Breach Clause 7.2**	**No appeal**	**Page 85**

PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, about sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the general public either directly or indirectly, including by means of the Internet
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Nicholas Browne QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 020 7930 9677 facsimile 020 7930 4554).