NUMBER 73 August 2011

CODE OF PRACTICE REVIEW

PMCPA 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 ABPI Code of Practice for the Pharmaceutical Industry independently of the Association itself.

ANNUAL REPORT FOR 2010

The Annual Report of the Prescription Medicines Code of Practice Authority for 2010 will be published shortly and copies will be sent to all who are on the mailing list for the Code of Practice Review. Further copies will be available on request.

There were 86 complaints in 2010 compared with 92 complaints in 2009.

The 86 complaints in 2010 gave rise to 78 cases. The number of cases generally differs from the number of complaints, the reason being that some complaints involve more than one respondent company and some complaints do not become cases at all, because they are not within the scope of the Code or they are withdrawn.

Of the 241 rulings made by the Code of Practice Panel in 2010, 197 (82%) were accepted by the parties, 27 (11%) were unsuccessfully appealed and 17 (7%) were successfully appealed. This compares with the 10% of rulings which were successfully appealed in 2009.

The Code of Practice Panel met 59 times in 2010 (79 in 2009) and the Code of Practice Appeal Board met 11 times in 2010 (9 in 2009). The Appeal Board considered appeals in 20 cases in 2010 compared to 15 in 2009.

The number of complaints made by pharmaceutical companies in 2010 exceeded the number made by health professionals, there being 23 from pharmaceutical companies and 21 from health professionals. This reversed the usual pattern of the last eight years when complaints from health professionals have been in the majority.

The Authority advertises brief details of all cases where companies were ruled in breach of Clause 2 of the Code, were required to issue a corrective statement or were the subject of a public reprimand. These advertisements act as a sanction and highlight what constitutes a serious breach of the Code.

Two, advertisements were placed in the BMJ, The Pharmaceutical Journal and the Nursing Standard in 2010 in relation to complaints received during the year and the remainder were published or will be published in 2011.

Copies of the advertisements are on the PMCPA website.

NEXT VERSION OF THE CODE

Changes have been agreed to the EFPIA (European Federation of Pharmaceutical Industries and Associations) Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Health Professionals and the EFPIA Code on Relationships between the Pharmaceutical Industry and Patient Organisations. The ABPI Code would have to be amended as a consequence of these changes. Proposals will be published in due course.

COMPANIES ATTENDING APPEAL

It was the Appeal Board's view that it was extremely helpful if companies attended when appealing cases to the Appeal Board.

TAKING AND PASSING THE ABPI EXAMINATIONS FOR REPRESENTIVES

Representatives have to take either the ABPI Medical Representatives Examination or the ABPI Generic Sales Representatives Examination, as appropriate, within their first year of such employment and have to pass it in full within two years. The one and two year periods are calculated on the basis of the time spent working as a representative, whether continuous or otherwise and whether with one company or more than one company.

The Director of the PMCPA is empowered by the supplementary information to Clause 16.3 of the Code of Practice to extend the one or two year periods in the event of extenuating circumstances such as prolonged illness or no or inadequate opportunity to take the examination.

If a representative fails to take the relevant examination within the first year it does not prevent he or she continuing to work as a representative in the second year. What it does mean is that in the absence of an agreed extension the company concerned would be in breach of Clause 16.3.

An application for an extension to the one year period should be made on a form available from the PMCPA. It should preferably be made by the company rather than the representative because it is the company which would breach the

Continued overleaf....

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 date on which places remain available is:
Monday, 3 October 2011

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 Nora Alexander for details (020 7747 1443 or email nalexander@pmcpa.org.uk).

HOW TO CONTACT THE AUTHORITY

Our address is:
Prescription Medicines Code of Practice Authority
7th Floor, Southside, 105 Victoria Street, London SW1E 6QT

www.pmcpa.org.uk

Telephone:	020 7747 8880
Facsimile:	020 7747 8881

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7747 8885 or email lmatthews@pmcpa.org.uk).

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
Ros Henley	020 7747 8883

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.

TAKING AND PASSING THE ABPI EXAMINATIONS FOR REPRESENTATIVES continued...

Code, not the representative. The application should be made before the one year period expires because, once it expires, the company is in breach of Clause 16.3 and Paragraph 5.6 of the PMCPA Constitution and Procedure would oblige the PMCPA Director to take the matter up as a complaint if told about it by the company.

The extenuating circumstances etc must relate to the particular representative rather than the company. A company cannot justify an extension by pleading, for example, that the problem arose because its systems were inadequate.

If a representative fails to pass the relevant examination within the two year period allowed he or she cannot continue to work as a representative and doing so in the absence of an extension would mean the company was in breach of Clause 16.3.

Here again, an application for an extension should be made on the form available from the PMCPA and should preferably be made by the company rather than the representative. The application should be made before the two years expires. As the representative's career is at stake in such circumstances, in considering an application for an extension the Director will, if possible, try to ensure that no individual is prejudiced by the failures of the employer.

Companies should have in place operating procedures which keep under review the examination status of all of their representatives, including contract representatives, and which can identify problems in advance of them happening. It appears from extension applications received that some companies do not have adequate procedures in this regard. Some companies seem to leave the matter to representatives themselves which is unsatisfactory because it is the companies which have to comply with the Code in this regard.

CASE AUTH/2378/12/10

PRIMARY CARE MEDICAL DIRECTOR v PFIZER

Promotion of Champix

A primary care medical director complained about the conduct of a Pfizer representative who presented at a smoking cessation meeting attended by approximately 60 smoking cessation advisors, who were non-clinical non-prescribers.

A colleague of the complainant attended the meeting. The complainant stated that part of the presentation promoting Champix (varenicline) underplayed the side effects of low mood and suicidal thoughts and attributed the suggested side effects to being similar to someone trying to stop eating chocolate. The complainant's colleague considered that the promotion of Champix had been unbalanced and the warnings attached to Champix had been grossly underplayed. He tried to make the point that chocolate did not come with a warning but that Champix did.

In general the complainant's colleague considered that it was grossly unprofessional to promote the medicine to such an impressionable audience, who did not have the knowledge to question the pharmaceutical representatives.

The complainant considered that the conduct of the representative fell outside the bounds of acceptable professional behaviour.

The detailed response from Pfizer is given below.

The Panel noted that the complainant had not attended the meeting at issue but had complained on behalf of a colleague who had. The purpose of the meeting was to discuss a new patient mental health questionnaire which smoking cessation advisors had to complete before referring smokers for Champix therapy. Not all of the attendees at the meeting were health professionals but they had all been trained to level 2 by the local NHS Stop Smoking Service to provide information on all stop smoking medicines. The Panel considered that in these circumstances it was not unreasonable to give clinical information about Champix. In the Panel's view it could be difficult when presenting to a mixed audience to ensure that no-one was misled. It was particularly important not to mislead with regard to side-effects.

The Panel examined the slides used at the meeting. One slide depicted nicotine binding and stimulation of dopamine and the satisfaction associated with smoking. The next slide referred to the effect of varenicline binding to the receptor and resulting in only a partial stimulation of dopamine release. The partial agonist action of varenicline was stated to provide relief from craving and withdrawal symptoms as the nicotine level declined in a quit attempt and by competing with nicotine to bind to the receptor it also reduced the pleasurable effects of smoking and potentially the risk of full relapse after a 'slip up'.

The next section of slides was entitled 'Varenicline Guidance, Efficacy and Safety Data'. This section included a slide headed 'Considerations for Prescribing Varenicline' which stated:

- **Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation and suicide attempt, has been reported in patients undergoing a smoking cessation attempt, including those with varenicline. Treatment should be discontinued if these symptoms occur, or if agitation or changes in behaviour occur that are of concern to the clinician, patient, family or caregivers, or if the patient develops suicidal ideation or suicidal behaviour[1]**
- **The safety and efficacy of varenicline in patients with serious psychiatric illness has not been established[1]**
- **Prescribers should advise their patients with a history of psychiatric illness (e.g. depression) that stopping smoking may exacerbate their condition[1]**
- **No clinically meaningful drug-drug interactions[1]**
- **Stopping smoking can result in physiological changes that may alter the pharmacokinetics or pharmacodynamics of some medicinal products, for which dosage adjustment may be necessary (e.g. theophylline, warfarin and insulin)**

Reference 1 was to the Champix SPC and the slide recommended consulting the SPC before prescribing.

The Panel noted that Section 4.4 of the Champix SPC firstly referred to the emergence of significant depressive symptomatology including suicidal ideation in patients attempting to quit with Champix not all of whom had stopped smoking on the emergence of symptoms. Secondly, it was stated that depressed mood, rarely including suicidal ideation and suicide attempt might be a symptom of nicotine withdrawal and that smoking cessation with or without pharmacotherapy had been associated with exacerbation of underlying psychiatric illness eg depression. The slide

detailed above, however, referred to the general psychological effects of quitting first and then to the effects associated with Champix. In the Panel's view, although the slide clearly referred to the psychological side effects of Champix, by reversing the order of the information from the SPC it had subtly changed the emphasis and increased the importance of side effects associated with quitting in relation to those associated with Champix. The Panel considered that the slide should have presented the information in the same order as the SPC.

The Panel noted the representative's account stated that when using the slide described above, she focused on the safety of Champix and suicide ideation, the quotation being taken from the slide and primarily from Gunnell *et al* (2009). The representative showed and offered the audience a copy of Gunnell *et al* and quoted from the paper 'there is no causal link between Champix and suicide ideation, but there is between stopping smoking and suicide ideation'. The representative stated that she made a point of stating that if Champix patients exhibited mood changes or an increase in aggressive behaviour, therapy should be immediately withdrawn.

The Panel noted that it was difficult to be certain about what had been said at the meeting. Clearly it would be unacceptable to liken the side effects of taking Champix with the effects of stopping eating chocolate. It was extremely important that representatives gave clear information particularly when presenting to an audience which included non health professionals. The representative submitted that the analogy used with regard to chocolate was in relation to the reduced dopamine release brought about by Champix and not directly in relation to its side effects of low mood and suicidal ideation. It appeared that the reference to chocolate was the representative's own idea; no such analogy was in any of the slides or briefing material. The Panel noted that the complainant's colleague had linked the reduced dopamine release to the side effects seen with Champix and in that regard had likened the side effects of Champix to the representative's comments about chocolate. When referring directly to side effects the representative had cited Gunnell *et al* and in quoting that paper had stated 'there is no causal link between Champix and suicide ideation'. In the Panel's view this statement was not consistent with the particulars listed in the Champix SPC which stated that suicide ideation had been reported in post-marketing experience.

Overall, the Panel considered that on the balance of probabilities the representative had underplayed the psychological side effects seen with Champix therapy. Although the reference to chocolate was not directly in association with the side effects of the medicine, the link could nonetheless be made. In the Panel's view the reference to chocolate could imply that the severity of psychological side effects was much less than it was in reality. The Panel considered that the representative had been misleading about the side effects of Champix therapy and in that regard it ruled breaches of the Code. The Panel did not consider that the representative had maintained a high standard of ethical conduct. A further breach of the Code was ruled.

Upon appeal by Pfizer the Appeal Board noted the Panel's comments about the Champix SPC. In addition the Appeal Board noted that the SPC stated that in many post-marketing cases, but not all, symptoms of significant depression (agitation, depressed mood, changes in behaviour/thinking that were of concern or the development of suicidal ideation or behaviour) resolved after discontinuation of varenicline.

The Appeal Board noted that the representative had referred to Gunnell *et al* in her presentation and was concerned to note from Pfizer's representatives at the appeal that this paper had not been approved for promotional use. In quoting from the paper the representative had stated that 'there is no causal link between Champix and suicide ideation'. Gunnell *et al*, however, had stated 'There was no evidence that varenicline was associated with an increased risk of … suicidal thoughts …'. The authors found no clear evidence of an increased risk of self harm associated with varenicline compared with other products although the limited study power meant that they could not rule out either a halving or a twofold increase in risk. The Appeal Board was concerned that the representative had thus presented the absence of evidence of a link between Champix and suicidal ideation as evidence of absence of a link. Pfizer's representatives at the appeal submitted that no clinical trial had been designed to establish whether there was a causal link between Champix and suicidal ideation. The Appeal Board was also concerned about the slide headed 'Considerations for prescribing varenicline' (slide eleven of the representative's slide set) (used as the representative referred to Gunnell *et al*) and questioned whether it gave a balanced overview of Section 4.4 of the Champix SPC. In particular the Appeal Board noted the heading to the slide read 'Considerations for prescribing varenicline' whereas Section 4.4 of the SPC was headed 'Special warnings and precautions for use'. Overall, the Appeal Board considered that the representative's interpretation of Gunnell *et al* had underplayed and in that regard misled the audience about a potentially serious adverse effect of Champix. The Appeal Board upheld the Panel's rulings of breaches of the Code.

The Appeal Board noted that the representative said she had referred to chocolate when using the slide showing the mechanism of action of varenicline to illustrate the effect of dopamine levels on mood. The Appeal Board considered that the complainant's comments in relation to

underplaying the warnings about Champix had been addressed in its rulings above.

The Appeal Board noted its rulings but, nonetheless, decided that the representative had not failed to maintain a high standard of ethical conduct. No breach of the Code was ruled in this regard.

A primary care medical director complained about the conduct of one of two representatives from Pfizer Limited who attended a local smoking cessation meeting.

COMPLAINT

The complainant stated that a colleague and two representatives from Pfizer were present at a stop smoking training event in November 2010 and the presentation was to approximately 60 smoking cessation advisors, who were non-clinical non-prescribers.

One of the Pfizer representatives promoted Champix (varenicline) but part of the presentation underplayed the side effects of low mood and suicidal thoughts and attributed the suggested side effects to being similar to someone trying to stop eating chocolate. The complainant's colleague considered that the promotion of Champix had been unbalanced and the warnings attached to Champix had been grossly underplayed. He tried to make the point that chocolate did not come with a warning but that Champix did.

In general the complainant's colleague considered that it was grossly unprofessional to promote the medicine to such an impressionable audience, who did not have the knowledge to question the pharmaceutical representatives.

The complainant considered that the conduct of the representative fell outside the bounds of acceptable professional behaviour.

When writing to Pfizer, the Authority asked it to respond in relation to Clauses 2, 7.2, 7.9 and 15.2 of the Code.

RESPONSE

Pfizer stated that the representative was invited to participate in the meeting. The local stop smoking service coordinator and organiser of the meeting told the representative that she could deliver a presentation on Champix to an audience of smoking cessation advisors. This was an audience of health professionals and appropriate administrative staff with specific expertise in smoking cessation including the non-pharmacological and pharmacological management of smokers to support their quit attempts. The purpose of the meeting was to discuss a new patient health questionnaire, the 'PHQ-9 Mental Health questionnaire' which the smoking cessation advisors had to complete before referring patients to receive Champix.

For the meeting, the representative selected and presented 16 slides taken from the master certified slide deck 'Smoking cessation and varenicline' (ref CHA841). The selected slides were considered appropriate for the specific audience and were unchanged from those of the master slide deck. The information contained in the slides presented was accurate and balanced. Copies of the presentation and of the master slide deck were provided.

Relevant to the topic of the meeting, Pfizer provided a copy of a comprehensive safety briefing document for the field force, 'Guidance on promotional activity for Champix (varenicline tartrate) in mental health' (ref CHA743). Pfizer submitted that the briefing document set out clear information for representatives about psychiatric and behavioural disorders and varenicline use. The slides headed 'Considerations for Prescribing Varenicline' dealt with these considerations and also referred the audience to the summary of product characteristics (SPC) before prescribing.

Those attending the meeting were trained smoking cessation advisors and included practice nurses, healthcare assistants, pharmacy technicians, school health workers/nurses and healthcare trainers. Two GPs also attended. An email from the meeting organizer confirmed that the audience had expertise in smoking cessation and had been trained to provide information on all stop smoking medicines. Copies of the emails were provided.

The presentation included slides headed 'The α4β2 Nicotinic Receptor is Key in the Addiction Pathway' and 'Varenicline: A Dual Mode of Action at the α4β2 Nicotinic Receptor' which discussed the mechanism of action of nicotine in the brain, in particular at the α4β2 nicotinic receptor and the physiological and psychological effects associated with the release of dopamine. The latter slide described the effect that varenicline had when it bound to the α4β2 nicotinic receptor and how this might help with symptoms of nicotine withdrawal and also reduce the rewarding effects of nicotine if a patient smoked whilst taking varenicline. In order to illustrate the association of dopamine release with pleasurable sensations, the representative used an analogy with a range of pleasurable external stimuli including eating chocolate. Her use of this analogy was not an attempt to link chocolate and Champix let alone to link any neuropsychiatric side effects of not eating chocolate to those of Champix.

The presentation at issue included a slide detailing the neuropsychiatric warnings and precautions from the Champix SPC and others which discussed the dosing of varenicline and the varenicline treatment course. The final slide was the Champix prescribing information.

Following the presentation, the representative heard that a member of the audience was concerned with the chocolate analogy used to

illustrate the association of dopamine release from nicotine and so she asked the meeting organiser if there was a need for clarification for the audience. In the organiser's view nothing misleading had been presented and there was no need for clarification. Furthermore, no other member of the audience had raised any concern.

In consideration of the above, Pfizer believed that no misleading information, claims or comparisons were made by the representative; the representative conducted herself in a professional and ethical manner and high standards were met. Pfizer thus denied breaches of Clauses 2, 7.2, 7.9 or 15.2. The representative, and her Pfizer colleague who also attended the meeting, had both passed the ABPI Medical Representatives Examination.

In response to a request for further information Pfizer stated that the presentation at issue was also the training presentation for representatives. There was no separate briefing document covering the training slide set.

PANEL RULING

The Panel noted that the complainant had not attended the meeting at issue but had complained on behalf of a colleague who had. The purpose of the meeting was to discuss a new patient mental health questionnaire which smoking cessation advisors had to complete before referring smokers for Champix therapy. Not all of the attendees at the meeting were health professionals but they had all been trained to level 2 by the local NHS Stop Smoking Service to provide information on all stop smoking medicines. The Panel considered that in these circumstances it was not unreasonable to give clinical information about Champix. The information had to be tailored towards the audience and otherwise comply with the Code. The representative had selected 16 slides which she considered were appropriate for the audience. In the Panel's view it could be difficult when presenting to a mixed audience to ensure that no-one was misled. It was particularly important not to mislead with regard to side-effects.

The Panel examined the slides used at the meeting. One slide depicted nicotine binding to the α4β2 nicotinic receptor and thus stimulating dopamine release which resulted in the satisfaction associated with smoking. The next slide referred to the effect of varenicline binding to the receptor and resulting in only a partial stimulation of dopamine release. The partial agonist action of varenicline was stated to provide relief from craving and withdrawal symptoms as the nicotine level declined in a quit attempt and by competing with nicotine to bind to the receptor it also reduced the pleasurable effects of smoking and potentially the risk of full relapse after a 'slip up'.

The next section of slides was entitled 'Varenicline Guidance, Efficacy and Safety Data'. This section included a slide headed 'Considerations for Prescribing Varenicline' which stated:

- Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation and suicide attempt, has been reported in patients undergoing a smoking cessation attempt, including those with varenicline. Treatment should be discontinued if these symptoms occur, or if agitation or changes in behaviour occur that are of concern to the clinician, patient, family or caregivers, or if the patient develops suicidal ideation or suicidal behaviour[1]

- The safety and efficacy of varenicline in patients with serious psychiatric illness has not been established[1]

- Prescribers should advise their patients with a history of psychiatric illness (e.g. depression) that stopping smoking may exacerbate their condition[1]

- No clinically meaningful drug-drug interactions[1]

- Stopping smoking can result in physiological changes that may alter the pharmacokinetics or pharmacodynamics of some medicinal products, for which dosage adjustment may be necessary (e.g. theophylline, warfarin and insulin)

Reference 1 was to the Champix SPC and the slide recommended consulting the SPC before prescribing.

The Panel noted that Section 4.4 of the SPC firstly referred to the emergence of significant depressive symptomatology including suicidal ideation in patients attempting to quit with Champix not all of whom had stopped smoking on the emergence of symptoms. Secondly, it was stated that depressed mood, rarely including suicidal ideation and suicide attempt might be a symptom of nicotine withdrawal and that smoking cessation with or without pharmacotherapy had been associated with exacerbation of underlying psychiatric illness eg depression. The slide detailed above, however, referred to the general psychological effects of quitting first and then to the effects associated with Champix. In the Panel's view, although the slide clearly referred to the psychological side effects of Champix, by reversing the order of the information from the SPC it had subtly changed the emphasis and increased the importance of side effects associated with quitting in relation to those associated with Champix. The Panel considered that the slide should have presented the information in the same order as the SPC.

The Panel noted that in the representative's account of the meeting, she had stated that when she used the slide described above, she focused on the safety of Champix and suicide ideation, the quotation being taken from the slide and primarily from Gunnell *et al* (2009). The representative

showed and offered the audience a copy of Gunnell *et al* and quoted from the paper 'there is no causal link between Champix and suicide ideation, but there is between stopping smoking and suicide ideation'. The representative stated that she made a point of stating that if Champix patients exhibited mood changes or an increase in aggressive behaviour, therapy should be immediately withdrawn.

The complainant had alleged that part of the presentation underplayed the side effects of low mood and suicidal thoughts attributing the suggested side effect to being similar to someone trying to stop eating chocolate. It was alleged that the promotion of Champix had been unbalanced and the associated warnings grossly underplayed. The colleague attending the meeting had tried to make the point that chocolate did not come with a warning whereas Champix did.

The Panel noted that it was very difficult to be certain about precisely what had been said at the meeting. Clearly it would be unacceptable to liken the side effects of taking Champix with the effects of stopping eating chocolate. It was extremely important that representatives gave clear information particularly when presenting to an audience which included non health professionals. The representative submitted that the analogy used with regard to chocolate was in relation to the reduced dopamine release brought about by Champix and not directly in relation to its side effects of low mood and suicidal ideation. It appeared that the reference to chocolate was the representative's own idea; no such analogy was in any of the slides or briefing material. The Panel noted that the complainant's colleague had linked the reduced dopamine release to the side effects seen with Champix and in that regard had likened the side effects of Champix to the representative's comments about chocolate. When referring directly to side effects the representative had cited Gunnell *et al* and in quoting that paper had stated 'there is no causal link between Champix and suicide ideation'. In the Panel's view this statement was not consistent with the particulars listed in the Champix SPC which stated that suicide ideation had been reported in post-marketing experience.

Overall, the Panel considered that on the balance of probabilities the representative had underplayed the psychological side effects seen with Champix therapy. Although the reference to chocolate was not directly in association with the side effects of the medicine, the link could nonetheless be made. In the Panel's view the reference to chocolate could imply that the severity of psychological side effects was much less than it was in reality. The Panel considered that the representative had been misleading about the side effects of Champix therapy and in that regard it ruled breaches of Clauses 7.2 and 7.9. The Panel did not consider that the representative had maintained a high standard of ethical conduct. A breach of Clause 15.2 was ruled.

The Panel noted its rulings above and considered that the representative's conduct was not such as to reduce confidence in, or bring disrepute upon, the industry. No breach of Clause 2 was ruled.

APPEAL BY PFIZER

Pfizer noted that this case arose from a meeting of a local smoking cessation service. The purpose of the meeting was to discuss the new PHQ-9 mental health questionnaire which smoking cessation advisors had to complete before they referred patients to receive Champix. The representative was invited to speak about Champix; other companies were also invited to participate and discuss their own products. Those attending the meeting were trained smoking cessation advisors including practice nurses, health assistants, pharmacy technicians, school health workers/nurses and health trainers. Two GPs also attended.

Pfizer submitted that at the meeting, the representative presented from the certified slide deck 'Smoking cessation and varenicline'. The representative presented sixteen slides which were taken from the master slide deck and these were considered appropriate for the specific audience. The focus of this presentation was the importance of smoking cessation, the mode of action of varenicline, how to prescribe varenicline and safety considerations, including warnings, precautions and drug interactions.

The slides discussed the mechanism of action of nicotine in the brain and the physiological and psychological effects associated with dopamine release. To help explain to the audience the pleasurable sensation created by dopamine release from smoking, an analogy was used to compare smoking with shopping, sex and eating chocolate. No link was made between chocolate and any medicine. The presentation went on to describe the dual mode of action of varenicline at the nicotinic receptor, and how this might help with symptoms of nicotine withdrawal (such as cravings) and also reduce the rewarding effects of nicotine if a cigarette was smoked during varenicline use.

The representative then presented 'Considerations for Prescribing Varenicline'; the slide included details of the Champix indication and contraindications and the statement 'Refer to the full Summary of Product Characteristics before prescribing'. The following slide detailed relevant safety information, warnings and precautions and interactions with other medicinal products. It stated 'Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation and suicide attempt, has been reported in patients undergoing a smoking cessation attempt, including those with varenicline. Treatment should be discontinued if these symptoms occur, or if agitation or changes in behaviour occur that are of concern to the

clinician, patient, family or caregivers, or if the patient develops suicidal ideation or suicidal behaviour. The safety and efficacy of varenicline in patients with serious psychiatric illness has not been established. Prescribers should advise their patients with a history of psychiatric illness (eg depression) that stopping smoking may exacerbate their condition'. This slide also had the statement 'Refer to the full Summary of Product Characteristics before prescribing'. The representative went on to discuss dosing guidance for Champix and the treatment course. The final slide was of the prescribing information.

Pfizer submitted that following the presentation, the representative became aware that a member of the audience was concerned with the chocolate analogy used to illustrate the association of dopamine release with pleasurable sensation. In response to this the representative asked the meeting organizer if there was a need for clarification for the audience. However, the organiser's view was that nothing misleading had been presented and therefore there was no need for clarification. Furthermore, no other member of the audience had raised any concern.

Pfizer noted that the complainant had not been at the meeting in question, but was writing on behalf of a colleague who had. The complaint was therefore not a first-hand account of what was presented at the meeting. The colleague who attended the meeting had not submitted a written complaint.

Pfizer noted that the Panel had noted that Section 4.4 of the SPC firstly referred to neuropsychiatric symptoms reported in post-marketing experience and secondly, symptoms associated with nicotine withdrawal with or without pharmacotherapy. The Panel also noted that the presentation referred to the general psychological effects of nicotine withdrawal first and then to the events reported in the post-marketing experience and considered that by reversing the order of this, it changed the emphasis and increased the importance of side effects associated with smoking cessation compared with those associated with varenicline. The Panel considered that the presentation should have discussed the information in the same order as the SPC.

Pfizer submitted that Section 4.4 of the SPC should be considered in its entirety and that the order of presenting the information did not emphasise one part over another. It was unreasonable to expect that, in a presentation about smoking cessation and the role of varenicline, the neuropsychiatric adverse events and varenicline should be discussed before the neuropsychiatric effects associated with smoking cessation overall. A significant body of evidence showed that smokers generally had a higher incidence of neuropsychiatric symptoms compared with non smokers and that smoking cessation itself, regardless of pharmacological intervention, could be associated with such symptoms. It seemed reasonable to present this context before discussing the safety profile of varenicline. In addition Pfizer noted that post-marketing experience of adverse events did not imply causality. Importantly no causal relationship had been established between varenicline and neuropsychiatric events. The representative very clearly presented and emphasised the warnings and precautions associated with Champix in Section 4.4 of the SPC, and the conditions under which treatment should be discontinued. Therefore it was not the case that greater importance was placed on any particular section of the SPC. The information was presented in its entirety, was accurate, balanced, and was not misleading.

Pfizer noted that the allegation that part of the presentation underplayed the side effects of varenicline, attributing the side effects to being similar to those that might occur when stopping eating chocolate. The Panel noted that it was difficult to be certain about precisely what had been said in the meeting. Pfizer submitted that it was difficult for the complainant as they were not at the meeting. However, Pfizer was clear that no comparison was made between the side effects of varenicline and stopping eating chocolate. In fact there was no link between chocolate and any pharmacological treatment. The analogy with chocolate (as another addictive substance) was simply to help explain the pleasurable sensation caused by dopamine release.

Pfizer submitted that this was an individual misunderstanding on the part of the complainant's colleague regarding the representative's presentation. Pfizer emphasised that the presentation contained a large amount of clear and detailed safety information from the Champix SPC. Furthermore, once the representative knew that one of the attendees might have misinterpreted what she had said, she offered to provide immediate clarification but was advised by the meeting organiser that her presentation was not misleading and therefore further clarification was not required. Confirmation of Pfizer's view could be sought from the meeting organiser and any of the other attendees at the meeting.

Pfizer noted that, in the Panel's view, reference to Gunnell *et al*, which analysed safety data from the UK General Practice Research Database (GPRD) database and could not demonstrate a causal link between varenicline and neuropsychiatric events, was not consistent with the particulars listed in the SPC. Pfizer emphasised that no causal link between the use of varenicline and neuropsychiatric events had been established, therefore the findings from Gunnell *et al* were consistent with the particulars of the SPC, which itself did not attribute any causal relationship with varenicline. As previously stated, post-marketing experience did not imply causality.

Pfizer submitted that in addition to Gunnell *et al*, no clinical trials or meta-analyses in the varenicline clinical programme had demonstrated a causal link between varenicline and neuropsychiatric events, and yet it would not be logical to dis-allow presentation of the safety information from this clinical data in promotional material on the basis that it did not demonstrate causality. The representative gave a balanced presentation. She discussed Gunnell *et al* and she presented the warnings and precautions from the SPC. She did not do one without the other. As there was no causal link within the SPC, the clinical data she presented was consistent with the SPC.

As explained above, Pfizer submitted that all information, claims and comparisons were accurate, balanced, fair, objective and unambiguous, based on an up-to-date evaluation of all evidence and reflected that evidence clearly. The representative had not misled the audience about the side effects of Champix and indeed reflected the particulars of the SPC throughout the meeting. Pfizer denied breaches of Clauses 7.2 and 7.9.

As evident from the accounts provided, Pfizer submitted that the representative conducted herself in a professional and ethical manner and that high standards were maintained before, during and after the meeting. Pfizer denied a breach of Clause 15.2.

In summary, Pfizer submitted that the Panel's rulings appeared to be based on comments made by an individual who was not at the meeting and the actual attendee had not submitted a written complaint. Pfizer provided the Panel with evidence of the slides presented and the representative's account of the discussions that took place. No link was made by the representative between eating chocolate and Champix. The presentation clearly discussed the safety profile, warnings and precautions for Champix as described in the SPC and was consistent with the SPC. The representative offered, at the time, to clarify any points that might have been misinterpreted by an individual attendee but this was not considered necessary. For the reasons stated above Pfizer submitted that the rulings of breaches of Clauses 7.2, 7.9 and 15.2 were unwarranted.

COMMENTS FROM THE COMPLAINANT

The complainant accepted Pfizer's assertion that he was not present at the meeting in question, however this matter was brought to his area prescribing committee as there were concerns about the way the presentation had represented Champix.

The complainant noted that the audience had two GPs who were the only prescribers. The rest were a mixture of non-clinical and nursing advisors, all of whom guided patients through the process of stopping smoking. The area prescribing committee considered that to mention chocolate that had no licence for prescribing, and Champix, a licensed medicine, in the same presentation seemed inappropriate. It potentially gave non-prescribers a false impression.

The complainant noted that the sole intention of the area prescribing committee was to draw this to the attention of the industry, to prevent this possible conflict occurring in other areas, and not to impune the reputation of Pfizer.

APPEAL BOARD RULING

The Appeal Board noted the Panel's comments about the Champix SPC. In addition the Appeal Board noted that the SPC stated that in many post-marketing cases, but not all, symptoms of significant depression (agitation, depressed mood, changes in behaviour/thinking that were of concern or the development of suicidal ideation or behaviour) resolved after discontinuation of varenicline.

The Appeal Board noted that the representative had referred to Gunnell *et al* in her presentation and was concerned to note from Pfizer's representatives at the appeal that this paper had not been approved for promotional use. In quoting from the paper the representative had stated that 'there is no causal link between Champix and suicide ideation'. Gunnell *et al*, however, had stated 'There was no evidence that varenicline was associated with an increased risk of … suicidal thoughts …'. The authors found no clear evidence of an increased risk of self harm associated with varenicline compared with other products although the limited study power meant that they could not rule out either a halving or a twofold increase in risk. The Appeal Board was concerned that the representative had thus presented the absence of evidence of a link between Champix and suicidal ideation as evidence of absence of a link. Pfizer's representatives at the appeal submitted that no clinical trial had been designed to establish whether there was a causal link between Champix and suicidal ideation. The Appeal Board was also concerned about the slide headed 'Considerations for prescribing varenicline' (slide eleven of the representative's slide set) (used as the representative referred to Gunnell *et al*) and questioned whether it gave a balanced overview of Section 4.4 of the Champix SPC. In particular the Appeal Board noted the heading to the slide read 'Considerations for prescribing varenicline' whereas Section 4.4 of the SPC was headed 'Special warnings and precautions for use'. Overall, the Appeal Board considered that the representative's interpretation of Gunnell *et al* had underplayed and in that regard misled the audience about a potentially serious adverse effect of Champix. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.9. The appeal on these points was unsuccessful.

The Appeal Board noted that the representative said she had referred to chocolate when using the slide showing the mechanism of action of varenicline to illustrate the effect of dopamine levels on mood. The Appeal Board considered that the complainant's comments in relation to underplaying the warnings about Champix had been addressed in its rulings above.

The Appeal Board noted its rulings but, nonetheless, decided that the representative had not failed to maintain a high standard of ethical conduct. No breach of Clause 15.2 was ruled. The appeal on this point was successful.

Complaint received	**23 December 2010**
Case completed	**16 May 2011**

MERZ v ALLERGAN

Promotion of Botox and alleged breach of undertaking

Merz Pharma complained about the promotion of Botox (botulinum toxin type A) by Allergan at the National Stroke Forum. Merz supplied Xeomin (also botulinum toxin type A). The exhibition panel at issue had been withdrawn.

Allergan's stand featured the claim 'No set dose ratio has been established between BoNT-A formulations' referenced to Benecke *et al* (2005), Roggenkamper *et al* (2006), Hunt and Clarke (2009), Dressler (2008) and Brown *et al* (2008). Merz alleged that the claim was misleading and could not be substantiated and was in breach of previous inter-company dialogue for the following reasons:

1 **Benecke *et al* and Roggenkamper *et al* both showed a successful change from Botox to Xeomin at a 1:1 clinical conversion ratio with no difference in efficacy.**

2 **Allergan had undertaken previously in inter-company dialogue, in June 2009, not to use Hunt and Clarke in any promotional material.**

3 **The PMCPA had ruled three times that the Hunt and Clarke data on three separate occasions did not reflect the clinical situation and was therefore misleading. Its use as a reference to justify a claim that 'no set ratio' had been established between Botox and Xeomin was contrary to the regulatory view and the evidence provided by several large clinical trials.**

4 **Dressler supported the view of the regulator and the large clinical trials that Xeomin and Botox were of equal potency and supported a set dose ratio of 1:1.**

5 **Brown *et al* suggested that the Xeomin was less potent than Botox, again using a pre-clinical mouse model. This was the same conclusion drawn by Hunt and Clarke and equally did not represent the clinical situation as recognised by the regulators and the Appeal Board.**

Merz alleged that as Allergan had not supported the claim with any references to Dysport (the third product on the market) the claim at issue was clearly a direct attack against Xeomin and the relative potency of Xeomin vs Botox

Xeomin had been compared to Botox in two large clinical trials at a 1:1 dose ratio and no difference had been detected between the products. This led the European Public Assessment Report (EPAR) for Xeomin to state:

> **'Taken altogether, the data from the non-clinical and clinical development program, which has been designed with support of Scientific Advice, provided sufficient evidence that a 1:1 dose ratio between XEOMIN and BOTOX with respect to efficacy and safety can be concluded and the adoption of the dosage which has been established for Botox is adequately justified. Against this background a further extensive dose-ranging program would not have been justifiable from an ethical point of view.'**

In addition to this, Bocouture (the same active ingredient as Xeomin) and Vistabel (the same active ingredient as Botox) were compared at a 1:1 dose ratio (Sattler *et al* 2010). This data in addition to the two other non-inferiority studies led to the SPC for Bocouture to state:

> **'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency.'**

There was clearly no doubt that the regulators considered the two products to be equipotent and the dosing regimen for Xeomin was chosen explicitly to mirror that of Botox. In Merz's view this opinion was reinforced recently by the Appeal Board in Cases AUTH/2335/7/10 and AUTH/2346/8/10. During inter-company dialogue Merz asked Allergan to clarify this position with a statement that outlined the regulatory and Appeal Board position; however Allergan declined to do and stated that it did not believe that this statement reflected the available clinical evidence. Given that Allergan did not accept the very clear positions of the Appeal Board and the regulator and refused to accept the clinical evidence, Merz had no doubt that it intended to continue its campaign that Xeomin was less potent than Botox, of which this exhibition stand was just one part.

This claim, however, appeared to be a continuation of Allergan's position as set out in its letter of 20 October 2010 to the PMCPA in Case AUTH/2346/8/10 that 'Botox and Xeomin are not equivalent'.

The claim now in question was misleading as the dose conversion ratio had been clearly established in large clinical trials between Botox and Xeomin as 1:1. The claim clearly suggested that no dose ratio had been established between any of the botulinum type A products and was therefore misleading and could not be substantiated. Merz was also extremely concerned that despite:

- **the ruling in Case AUTH/2183/11/08 and its undertaking,**
- **the assurance in a letter to Merz of 24 June 2009 that the data would not be used in promotion following repeat usage**
- **assurances issued to Merz following inter-company dialogue on 21 October 2010**
- **the breaches of undertaking identified in Cases AUTH/2335/7/10 and AUTH/2346/8/10 and associated undertakings,**

Allergan repeatedly used the Hunt and Clarke data to suggest that Xeomin and Botox had different potencies; the claim at the National Stroke Forum was no exception. Whilst Allergan had agreed to not use this reference for this particular claim, Merz considered that Allergan did not take its undertakings to either Merz or the PMCPA seriously and would continue to use this data to support the misleading assertion that there was a difference in potencies between the products.

The detailed response from Allergan is given below.

The Panel noted that the prominent claim 'Unit doses of botulinum toxins are not interchangeable from one product to another' appeared in a highlighted orange box at the top of the exhibition panel above the heading 'Botox is a homogeneous 900kDa botulinum toxin'. Beneath were 3 bullet points including: 'No set dose ratio has been established between BoNT-A formulations'; 'The SmPCs of all BoNT-A products carry the same statement "The unit doses of … are specific to the preparation and are not interchangeable with other preparations of botulinum toxin"'. The words 'No set dose' and 'not interchangeable' appeared in prominent orange font such that, in the Panel's view, they would be the take home message for delegates. The Panel noted that whilst the exhibition panel did not mention stroke, it was displayed at the National Stroke Forum and thus delegates would assume that the data therein were relevant to its use in stroke patients.

The Panel noted Merz's comments about the statement in the Bocouture SPC that comparative clinical study results suggested that Bocouture and the comparative product containing conventional Botulinum toxin type A complex (900KD) were of equal potency. This appeared beneath the general statement in the SPC that unit doses recommended for Bocouture were not interchangeable with those for other preparations of Botulinum toxin. The Panel noted that Bocouture was only indicated for the temporary improvement in the appearance of moderate to severe vertical lines between the eyebrows seen at frown (glabellar frown lines) in adults below 65 years when the severity of these lines had an important psychological impact for the patient. Xeomin and Botox had different indications.

The Panel noted the parties' submissions about the products' clinical conversion ratio and efficacy as evidenced by Benecke *et al* and Roggenkamper *et al*. The Panel noted the Xeomin EPAR stated that the non clinical and clinical development programme provided sufficient evidence that a 1:1 dose ratio between Xeomin and Botox with respect to efficacy and safety could be concluded. This was not included in the SPC. There was data showing non inferiority of the products in certain indications. However the Panel noted the differences between the Botox and Xeomin SPCs in relation to post-stroke spasticity, including the wording of the indication, the recommended muscles and dose ranges and the maximum total recommended doses (based on the clinical trials submitted to gain approval) as submitted by Allergan. The exact dose and the number and location of injection sites needed to be tailored to the individual patient. Each SPC stated that unit doses of botulinum toxins were not interchangeable from one product to another. The Panel considered that the claim 'No set dosing ratio has been established' was not an unreasonable reflection of the totality of the evidence; it was not misleading nor incapable of substantiation as alleged. No breach of the Code was ruled.

The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings.

In relation to the reference to Hunt and Clarke (2009) and Allergan's alleged failure to implement an inter-company agreement with Merz, the Director noted that Allergan stated that it had reviewed all its current materials both manually and by audit of its electronic copy approval repository. No other promotional materials referred to Hunt and Clarke. The exhibition panel now at issue had been withdrawn. The Director considered that this aspect of the complaint had been resolved via inter-company dialogue and thus it was not referred to the Panel.

With regard to the alleged breach of undertakings in the previous cases, Cases AUTH/2183/11/08, AUTH/2335/7/10 and AUTH/2346/8/10 the Panel noted that Cases AUTH/2335/7/10 and AUTH/2346/8/10 related to claims about differences in potency between Xeomin and Botox based on Hunt and Clarke. The Appeal Board had ruled breaches of the undertaking given in Case AUTH/2183/11/08 due to the use of Hunt and Clarke to imply that Botox was more potent than Xeomin. The Panel considered that the material at issue in Case AUTH/2380/1/11 was sufficiently different for it not to be covered by the previous undertakings. The claim at issue did not refer to potency, nor did it imply an advantage for Botox. In addition the statement from the SPC was included on the poster. Another relevant factor was that the poster was used at the National Stroke Forum and there were differences between Xeomin and Botox

in relation to the indications and doses for post-stroke spasticity. The Panel ruled that the claim at issue was not in breach of the undertakings given in Cases AUTH/2335/7/10 and AUTH/2346/8/10. No breach of the Code was ruled.

Merz Pharma UK Ltd complained about the promotion of Botox (botulinum toxin type A) by Allergan Limited at the National Stroke Forum which took place in Glasgow between 30 November and 2 December 2010. Merz Pharma supplied Xeomin (also botulinum toxin type A). Inter-company dialogue had resolved some but not all matters at issue. The exhibition panel at issue had been withdrawn.

COMPLAINT

Merz stated that Allergan's promotional stand at the meeting in question featured the claim 'No set dose ratio has been established between BoNT-A formulations' referenced to Benecke *et al* (2005), Roggenkamper *et al* (2006), Hunt and Clarke (2009), Dressler (2008) and Brown *et al* (2008). Merz alleged that the claim was misleading and could not be substantiated and was in breach of previous inter-company dialogue for the following reasons:

1 Benecke *et al* and Roggenkamper *et al* both showed a successful change from Botox to Xeomin at a 1:1 clinical conversion ratio with no difference in efficacy.

2 Allergan had undertaken previously in inter-company dialogue, in a letter of 24 June 2009, not to use Hunt and Clarke 'Specifically, the study by Hunt *et al* will not be used in any promotional material ...'. This was clearly using this data in a promotional setting and Merz required Allergan to abide by its previous undertaking.

3 The PMCPA had ruled three times that the Hunt and Clarke data on three separate occasions did not to reflect the clinical situation and was therefore misleading. Its use as a reference to justify a claim that 'no set ratio' had been established between Botox and Xeomin was contrary to the regulatory view and the evidence provided by several large clinical trials.

4 Dressler supported the view of the regulator and the large clinical trials that Xeomin and Botox were of equal potency and supported a set dose ratio of 1:1.

5 Brown *et al* suggested that the Xeomin was less potent than Botox, again using a pre-clinical mouse model. This was the same conclusion drawn by Hunt and Clarke and equally did not represent the clinical situation as recognised by the regulators and the Appeal Board.

Merz alleged that as Allergan had not supported the claim with any references to Dysport, the claim at issue was clearly a direct attack against Xeomin and the relative potency of Xeomin vs Botox.

It remained the case that Xeomin had been compared to Botox in two large clinical trials at a 1:1 dose ratio and no difference had been detected between the products. This led the European Public Assessment Report (EPAR) for Xeomin to state:

> 'Taken altogether, the data from the non-clinical and clinical development program, which has been designed with support of Scientific Advice, provided sufficient evidence that a 1:1 dose ratio between XEOMIN and BOTOX with respect to efficacy and safety can be concluded and the adoption of the dosage which has been established for Botox is adequately justified. Against this background a further extensive dose-ranging program would not have been justifiable from an ethical point of view.'

In addition to this, Bocouture (the same active ingredient as Xeomin) and Vistabel (the same active ingredient as Botox) were compared at a 1:1 dose ratio (Sattler *et al* 2010). This data in addition to the two other non-inferiority studies led to the SPC for Bocouture to state:

> 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency.'

There was clearly no doubt that the regulators considered the two products to be equipotent and the dosing regimen for Xeomin was chosen explicitly to mirror that of Botox. In Merz's view this opinion was reinforced recently by the Appeal Board in Cases AUTH/2335/7/10 and AUTH/2346/8/10. During inter-company dialogue Merz asked Allergan to clarify this position with a statement that outlined the regulatory and Appeal Board position; however Allergan declined to do and stated that it did not believe that this statement reflected the available clinical evidence. Allergan repeatedly refused to accept the conclusions of the clinical data, the regulator and now the Appeal Board without providing any argument or evidence to support its position. Given that Allergan did not accept the very clear positions of the Appeal Board and the regulator and refused to accept the clinical evidence, Merz had no doubt that it intended to continue its campaign that Xeomin was less potent than Botox, of which this exhibition stand was just one part.

This claim, however, appeared to be a continuation of the statement contained in Allergan's letter of 20 October 2010 to the PMCPA in response to Merz's appeal in Case AUTH/2346/8/10. Wherein Allergan made it clear that its position was that 'Botox and Xeomin are not equivalent'.

The claim in question as presented at the National Stroke Forum was misleading as the dose conversion ratio had been clearly established in large clinical trials between Botox and Xeomin as 1:1. The inclusion of a reference to Dysport SPC would detract from the fact that a dose ratio had been determined between Botox and Xeomin. The

claim clearly suggested that no dose ratio had been established between any of the botulinum type A products and was therefore misleading and could not be substantiated. Merz alleged breaches of Clauses 7.2 and 7.4.

Merz was also extremely concerned that despite:

- the ruling in Case AUTH/2183/11/08 and its undertaking,
- the assurance in a letter to Merz of 24 June 2009 that the data would not be used in promotion following repeat usage
- assurances issued to Merz following inter-company dialogue on 21 October 2010
- the breaches of undertaking identified in Cases AUTH/2335/7/10 and AUTH/2346/8/10 and associated undertakings

Allergan repeatedly used the Hunt and Clarke data to suggest that Xeomin and Botox had different potencies; the claim at the National Stroke Forum was no exception. Whilst Allergan had agreed to not use this reference for this particular claim, Merz considered that Allergan did not take its undertakings to either Merz or the PMCPA seriously and would continue to use this data to support the misleading assertion that there was a difference in potencies between the products.

When writing to Allergan, the Authority asked it to respond in relation to Clauses 2, 9.1 and 25 of the 2008 Code in addition to the clauses cited by Merz.

RESPONSE

Allergan stated that it did not consider that the claim, 'No set dose ratio has been established between BoNT-A formulations', was misleading or incapable of substantiation. The claim was clearly supported by the heading, 'Unit doses of botulinum toxins are not interchangeable from one product to another' and the subsequent bullet point, 'The SmPCs of all BoNT-A products carry the same statement: "The unit doses of … are specific to the preparation and are not interchangeable with other preparations of botulinum toxin"'.

As was established by the Appeal Board in Case AUTH/2270/10/09, both Allergan and Merz agreed that Benecke *et al* and Roggenkamper *et al* were non-inferiority studies which showed Xeomin was no worse than Botox by a pre-specified margin (delta) that was clinically acceptable. The Appeal Board noted Merz's submission that it had no data upon which to make the claim that Xeomin was equivalent to Botox. Therefore, Benecke *et al* and Roggenkamper *et al* did not support a '… 1:1 clinical conversion ratio with no difference in efficacy' as submitted by Merz. Clearly a 1:1 dosing ratio was chosen in these two studies in cervical dystonia and blepharospasm but this was not 'a set dose ratio' across all indications.

The claim regarding 'no set dose ratio' was contextualised as discussed above and the heading and bullet point referenced the SPCs for Botox, Xeomin and Dysport.

The recommended SPC dosing for Botox, Dysport and Xeomin clearly indicated that the starting and maximum doses were different across indications and that there was no set dose ratio between the products. Importantly all three also had different licensed indications.

More specifically, there were very clear differences in the SPCs for Botox and Xeomin with respect to post stroke spasticity, the most relevant indication for clinicians attending the National Stroke Forum. These differences were outlined in the table provided but included differences in the wording of the indication, the recommended muscles and dose ranges and the maximum total recommended doses (based on the clinical trials submitted to gain licence approval). When comparing the Botox and Xeomin SPCs with the SPC for Dysport, across all indications, including post stroke spasticity, these differences were even more apparent. However, what was clear across all the SPCs and the various indications was that the exact dose and the number and location of injections sites needed to be tailored to the individual patient and titrated to effect.

As stated in section 4.2 of the Xeomin SPC:

> 'The optimum dosage and number of injection sites in the treated muscle should be determined by the physician individually for each patient. A titration of the dose should be performed.'
>
> 'The exact dosage and number of injection sites should be tailored to the individual patient based on the size, number and location of muscles involved, the severity of spasticity, and the presence of local muscle weakness.'

These were a selection of the statements made on this theme, many similar statements could be found in the Botox and Dysport SPCs.

When considering these statements, in addition to the clear statement in all three SPCs that unit doses of botulinum toxins were not interchangeable from one product to another, Merz's assertion that there was a set dose ratio between Botox and Xeomin was incorrect and not in line with the SPCs.

Allergan thus did not believe the claim was in breach of either Clauses 7.2 or 7.4.
Whilst Allergan did not believe the claim was misleading or incapable of substantiation it acknowledged that the claim referenced Hunt and Clarke which was not in accordance with the inter-company dialogue agreement. Allergan acknowledged this error in its letter to Merz of 20 December 2010, and it had withdrawn the stand panel at issue. Allergan took this error in referencing very seriously, it had reviewed all of its promotional materials and no other promotional materials referred to Hunt and Clarke or Brown *et al*.

Allergan submitted that this was human error not a 'direct attack' against Xeomin and the relative potency of Xeomin vs Botox. Regarding the assertion that Allergan had deliberately excluded reference to Dysport, this was clearly not so as it had twice referenced the Dysport SPC on the exhibition panel.

Allergan believed the claim 'No set dose ratio has been established between BoNT-A formulations' was supported by reference to the product SPCs, as outlined above. Allergan could not agree that these were 'irrelevant' references for the reasons outlined above.

Merz incorrectly stated that a dose ratio had been clearly established between Botox and Xeomin of 1:1. In support of this argument it cited Benecke *et al* and Roggenkamper *et al*, non-inferiority studies which showed Xeomin was no worse than Botox by a pre-specified margin (delta) that was clinically acceptable. As discussed, earlier, a 1:1 dosing ratio was chosen in both studies but this did not mean there was 'a set dose ratio' of 1:1 for Botox and Xeomin across all indications.

In further support of its argument of a set dose ratio between Botox and Xeomin, Merz cited the Bocouture SPC. The statement in the Bocouture SPC that: 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900kD) are of equal potency' reflected the results of the Merz non-inferiority study conducted to gain approval of Merz's botulinum toxin for glabellar lines. A similar statement regarding the European therapeutic non-inferiority studies in cervical dystonia and blepharospasm (Benecke *et al*; Roggenkamper *et al*) was not contained in the Xeomin SPC. Therefore, Allergan failed to see how this statement for Bocouture supported a set dose ratio for Xeomin.

Allergan noted that the Bocouture SPC stated:

> 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.'

In addition, there were differences in the recommended dosing schedules for Bocouture and Vistabel (Allergan's botulinum toxin type A licensed for management of glabellar lines), in that the Bocouture SPC suggested an increase to 30 units, if required. This statement was not in the Vistabel SPC.

> ***Bocouture SPC:*** 'After reconstitution of Bocouture (50 units/1.25ml) the recommended injection volume of 0.1ml (4 units) is injected into each of the 5 injection sites: two injections in each corrugator muscle and one injection in the procerus muscle, which corresponds to a standard dose of 20 units. The dose may be increased by the physician to up to 30 units if required by the individual needs of the patients, with at least '3-months' interval between treatments.'
>
> ***Vistabel SPC:*** 'Reconstituted VISTABEL (50 U/1.25ml) is injected using a sterile 30 gauge needle. 0.1ml (4 U) is administered in each of the 5 injection sites: 2 injections in each corrugator muscle and 1 injection in the procerus muscle for a total dose of 20 U.'

In summary, as stated earlier, the exhibition panel and claim at issue, had been withdrawn from use. Allergan confirmed that if the claim, or a similar, was used in the future, it would directly reference all the SPCs for all the relevant botulinum toxin type A formulations. As the claim and the item at issue were not in use, Allergan considered inter-company dialogue on this matter was concluded.

The incorrect citation of Hunt and Clarke and Brown *et al* was simply human error, not part of a 'direct attack' on Xeomin.

However, as discussed above, the assertion by Merz that there was a set dose ratio between Botox and Xeomin was incorrect and not in line with the product SPCs.

Therefore, Allergan did not believe the claim was in breach of either Clauses 7.2 or 7.4.

Allergan strongly denied the allegation that it had breached the undertaking given in Case AUTH/2183/11/08.

As discussed earlier, the claim at issue 'No set dose ratio has been established between BoNT-A formulations' was an accurate reflection of the SPCs for the botulinum toxin type A products on the market. There was no suggestion or statement relating to differences in potencies between Botox and Xeomin.

Whilst Allergan did not believe the claim was misleading or incapable of substantiation it acknowledged that the claim referenced Hunt and Clarke which was not in accordance with the inter-company agreement. Allergan acknowledged this error in its letter to Merz dated 20 December 2010, and it had withdrawn the exhibition panel at issue. Allergan took this error in referencing very seriously. It had thoroughly reviewed all of its current promotional materials using both a manual check and an audit of its electronic copy approval repository (Zinc). Allergan submitted that no other promotional materials referred to Hunt and Clarke or Brown *et al*. Allergan believed it had maintained high standards by acting swiftly in this matter. Allergan had made all best efforts to resolve this matter via inter-company dialogue.

Allergan believed it had maintained high standards and had complied with its undertaking with respect to Case AUTH/2183/11/08. Allergan denied breaches of Clauses 2, 9.1 or 25.

PANEL RULING

The Panel noted that the prominent claim 'Unit doses of botulinum toxins are not interchangeable from one product to another' appeared in a highlighted orange box at the top of the exhibition panel above the heading 'Botox is a homogeneous 900kDa botulinum toxin'. Beneath were 3 bullet points including: '**No set dose** ratio has been established between BoNT-A formulations'; 'The SmPCs of all BoNT-A products carry the same statement "The unit doses of … are specific to the preparation and are **not interchangeable** with other preparations of botulinum toxin"'. The words 'No set dose' and 'not interchangeable' appeared in prominent orange font such that, in the Panel's view, they would be the take home message for delegates. The Panel noted that whilst the exhibition panel did not mention stroke, it was displayed at the National Stroke Forum and thus delegates would assume that the data therein were relevant to its use in stroke patients.

The Panel noted Merz's comments about the statement in the Bocouture SPC that comparative clinical study results suggested that Bocouture and the comparative product containing conventional Botulinum toxin type A complex (900KD) were of equal potency. This appeared beneath the general statement in the SPC that unit doses recommended for Bocouture were not interchangeable with those for other preparations of Botulinum toxin. The Panel noted that Bocouture was only indicated for the temporary improvement in the appearance of moderate to severe vertical lines between the eyebrows seen at frown (glabellar frown lines) in adults below 65 years when the severity of these lines had an important psychological impact for the patient. Xeomin and Botox had different indications.

The Panel noted the parties' submissions about the products' clinical conversion ratio and efficacy as evidenced by Benecke *et al* and Roggenkamper *et al*. The Panel noted the Xeomin EPAR stated that the non clinical and clinical development programme provided sufficient evidence that a 1:1 dose ratio between Xeomin and Botox with respect to efficacy and safety could be concluded. This was not included in the SPC. There was data showing non inferiority of the products in certain indications. However the Panel noted the differences between the Botox and Xeomin SPCs in relation to post-stroke spasticity, including the wording of the indication, the recommended muscles and dose ranges and the maximum total recommended doses (based on the clinical trials submitted to gain approval) as submitted by Allergan. The exact dose and the number and location of injection sites needed to be tailored to the individual patient. Each SPC stated that unit doses of botulinum toxins were not interchangeable from one product to another. The Panel considered that the claim 'No set dosing ratio has been established' was not an unreasonable reflection of the totality of the evidence; it was not misleading nor incapable of substantiation as alleged. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings.

With regard to the alleged breach of undertakings in the previous cases, Cases AUTH/2183/11/08, AUTH/2335/7/10 and AUTH/2346/8/10 the Panel noted that Cases AUTH/2335/7/10 and AUTH/2346/8/10 related to claims about differences in potency between Xeomin and Botox based on Hunt and Clarke. The Appeal Board had ruled breaches of the undertaking given in Case AUTH/2183/11/08 due to the use of Hunt and Clarke to imply that Botox was more potent than Xeomin. The Panel considered that the material at issue in Case AUTH/2380/1/11 was sufficiently different for it not to be covered by the previous undertakings. The claim at issue did not refer to potency, nor did it imply an advantage for Botox. In addition the statement from the SPC was included on the poster. Another relevant factor was that the poster was used at the National Stroke Forum and there were differences between Xeomin and Botox in relation to the indications and doses for post-stroke spasticity. The Panel ruled that the claim at issue was not in breach of the undertakings given in Cases AUTH/2335/7/10 and AUTH/2346/8/10. No breaches of Clauses 2, 9.1 and 25 were ruled.

Complaint received **4 January 2011**

Case completed **10 May 2011**

GENERAL PRACTITIONER v NOVO NORDISK

Articles in Daily Mail

A general practitioner complained about articles in the Daily Mail which referred to liraglutide (Victoza) marketed by Novo Nordisk. Victoza was indicated for the treatment of adults with type 2 diabetes to achieve glycaemic control in combination with oral anti-hyperglycaemics.

The complainant alleged that in a Daily Mail online article the managing director of Novo Nordisk promoted liraglutide as a treatment for weight reduction, for which it was not licensed. His claims of phenomenal study results were exaggerated and disparaged orlistat, which was licensed as a weight loss agent. He also stated that liraglutide could cure diabetes and that its effects on confidence and health were life-changing!! Liraglutide was not a dieting medicine let alone an antihypertensive or lipid modifying agent as stated. The complainant alleged that this sort of irresponsible and disguised promotion only raised unfounded hopes.

The complainant also referred to a second article in which experts and opinion leaders, no doubt supported by Novo Nordisk, advocated or promoted liraglutide as a treatment for weight loss.

This was similar to previous rulings involving Novo Nordisk (Cases AUTH/2202/1/09 and AUTH/2234/5/09) and the complainant asked what was the point of the Authority ruling a breach of the Code including Clause 2 or imposing any other sanction on the company.

The detailed response from Novo Nordisk is given below.

The Panel noted that the complainant referred to an article published on 27 December 2010 in the Mail Online which described liraglutide as a diet drug that could be available in three years and as a jab that had produced phenomenal results. It was stated to be 'More than twice as good as anything on the market'. The article explained that liraglutide 'lowers blood pressure, raises "good" cholesterol and can prevent and even cure diabetes'. Its current use in diabetes was mentioned as was the ongoing trial programme in obese men and women. Comparative data with orlistat, a medicine licensed for weight loss, was discussed which appeared to have been taken from Astrup *et al* (2009) and which was provided to the Daily Mail journalist at her request. The Novo Nordisk managing director was quoted as stating 'We have had phenomenal results from the first clinical trials in obesity' and 'that the effects on confidence and health were life-changing'. The article also featured quotations from an academic expert in hormones and weight loss.

The Panel noted that Novo Nordisk's PR agency had developed a media programme to raise the profile of Novo Nordisk and strengthen its relationships with journalists. Meetings on varying topics had been arranged with individual journalists. In the Panel's view, the selection of such journalists should stand up to scrutiny; it might be unacceptable to select a journalist who had repeatedly published material related to the subject matter of a proposed meeting which was inconsistent with the Code. In its draft proposal for the media programme, Novo Nordisk's agent had listed as potential topics for discussion with the Daily Mail journalist, modern life with diabetes, how treatments were evolving to improve day-to-day lives of patients and the future of diabetes (pipeline).

The Panel noted that Novo Nordisk's agency had arranged a meeting with the journalist to discuss the human, social and financial impact of diabetes and Novo Nordisk's heritage with diabetes care. Slide 15 of the presentation delivered at the meeting described the company's range of rapid-acting, long-acting and pre-mixed insulin although no brand names were mentioned. The following slide was headed 'GLP-1 receptor agonist': whilst not mentioning liraglutide by name it was described as a treatment for type 2 diabetes as an adjunct to diet and exercise in combination with specified anti-diabetic tablets. Slide 17 headed 'Addressing future diabetes care needs' listed 'Next generation insulin analogues', 'Incretin therapies', 'Oral insulin and oral GLP-1' and 'A cure for Type 1 diabetes'. None of the slides mentioned obesity. The presentation concluded by a discussion of work undertaken by Novo Nordisk to change diabetes through partnerships, access and quality of life. Slide 22 detailed Novo Nordisk's impact on 6 quality of life parameters for people with diabetes: the second bullet point read 'Only company with a once-daily GLP-1 analogue'. The Panel queried whether, given the stated aim of the meeting, the presentation had included disproportionate emphasis on liraglutide.

The Panel noted that the meeting notes detailed a general discussion but did not appear to cover the presentation. The Panel had no way of knowing precisely what was said about the slides.

The meeting notes showed that the journalist knew a lot about liraglutide from the European Obesity Conference and had also written about it on publication of the recommendation from the National Institute for health and Clinical Excellence (NICE) [for its use in diabetes]. The journalist requested information on how liraglutide worked,

its mode of action and trials for obesity and timelines. The journalist was told she would be provided with a liraglutide backgrounder and published obesity trial results (Astrup *et al*). The journalist later asked about the timelines of getting liraglutide on the market for obesity and was told that a rough timeline might be three years. According to the meeting notes when the journalist referred to liraglutide and obesity the Novo Nordisk representatives steered the conversation back to the original topic. Although the Panel was concerned that liraglutide was the only specific medicine mentioned it did not appear from either the presentation or the meeting notes that the request about liraglutide and obesity was solicited by Novo Nordisk.

The Panel had some concerns about the arrangements, presentation and discussion as set out above. Nonetheless the Panel did not consider that, on the evidence before it, the presentation, discussion and material provided to the journalist promoted a prescription only medicine to the public as alleged. No breach of the Code was ruled. Nor, on balance, did the Panel consider that the material provided was not factual or balanced in relation to the licensed indication for liraglutide, nor did it otherwise encourage a member of the public to seek a prescription for it. Novo Nordisk did not proactively provide information on liraglutide and obesity. No breach of the Code was ruled.

The Panel noted the complainant's reference to Cases AUTH/2202/1/09 and AUTH/2234/5/09, wherein breaches of the Code had been ruled and additional sanctions imposed in relation to the pre-licence promotion of liraglutide and its promotion to the public. Turning to the present case, Case AUTH/2382/1/11, the Panel noted its rulings of no breach of the Code above and thus ruled no breach of the Code including Clause 2.

A general practitioner complained about articles in the Daily Mail which referred to liraglutide (Victoza) marketed by Novo Nordisk Limited. Victoza was indicated for the treatment of adults with type 2 diabetes to achieve glycaemic control in combination with oral anti-hyperglycaemics.

COMPLAINT

The complainant stated that he had read, with interest, the rulings of the Authority advertised in the December 2010 issue of the Pharmaceutical Journal and noted, in particular, the prominence of Novo Nordisk in this regard. However, it appeared that the sanctions applied by the Authority had not had any great impact on Novo Nordisk's ongoing activities when it came to promoting prescription medicines to the public.

On 19 January 2011, the complainant read an article in the Daily Mail online [http://www.dailymail.co.uk/health/article-1341818/Jab-help-drop-dress-sizes-months.html] in which the managing director of Novo Nordisk clearly promoted the use of liraglutide as a treatment for weight reduction, for which it was not licensed. His claims of phenomenal study results reported for liraglutide were exaggerated and disparaged orlistat, which was licensed as a weight loss agent, and went beyond the pale by stating that liraglutide could cure diabetes and that its effects on confidence and health were life-changing!! Liraglutide was not a dieting medicine let alone an antihypertensive or lipid modifying agent as stated. The complainant alleged that this sort of irresponsible and disguised promotion only served to raise unfounded hopes. It was clear that this article appeared in print during December 2010 and was one of several such articles.

The complainant noted a second article [http://www.dailymail.co.uk/home/search.html?searchPhrase=liraglutide] which involved so-called experts and opinion leaders, no doubt supported by Novo Nordisk, who advocated or promoted the off-licence use of liraglutide as a treatment for weight loss.

This all seemed reminiscent of previous rulings against Novo Nordisk (Cases AUTH/2202/1/09 and AUTH/2234/5/09) and the complainant asked what was the point of the Authority ruling a breach of Clauses 2 and 9.1 or any other clause, or imposing any other sanction on the company.

When writing to Novo Nordisk, the Authority asked it to respond in relation to Clauses 2, 9.1, 22.1 and 22.2 of the Code.

RESPONSE

Novo Nordisk stated that its communications team had recently embarked upon a series of meetings with key journalists in the consumer media to raise the profile of Novo Nordisk and the wider diabetes pandemic. It was hoped that following these meetings, journalists would write an article or articles on the issues surrounding diabetes in order to increase the public's awareness and understanding of diabetes. These meetings were not arranged to create a platform from which to promote Victoza or any other Novo Nordisk product to the public.

Novo Nordisk's media agency arranged a meeting between its managing director, a Daily Mail journalist and a member of the communications team to discuss the human, social and financial impact of diabetes in the UK and Novo Nordisk's heritage within diabetes care. This meeting took place on Thursday, 11 November 2010.

A certified slide deck was used as a conversation piece for the meeting. This included information on the Novo Nordisk strategy, the triple bottom line principles (balancing Novo Nordisk's financial return with social and environmental commitments) and the growing diabetes pandemic which provided some published and approved facts and figures. During the discussion, the journalist stated that she

knew quite a lot about liraglutide and that she had independently attended the European Obesity Conference. The journalist then asked about the clinical trials for the use of liraglutide in obesity and what information Novo Nordisk could share. Novo Nordisk agreed to send a written statement on the liraglutide obesity trials, but could not discuss it within the scope of the meeting. On a couple of occasions throughout the meeting, the journalist asked for this information and each time Novo Nordisk stated that it would send her the appropriate published information at a later date and then brought the meeting back to the subject of highlighting the impact of diabetes. This was detailed within the minutes of the meeting which were written by a member of the communications team. A redacted copy was provided.

At the close of the meeting, the journalist was told that if she were to write an article on diabetes or would like more information on current diabetes statistics, or a quotation from the company then she would be welcome to contact the communications team. Novo Nordisk also asked to review any quotations she intended to use before publication.

Following the meeting, the journalist emailed the member of the communications team who had attended the meeting to ask for information on the mode of action of Victoza. A certified document entitled 'Incretin Backgounder' was sent to the journalist on 23 November 2010. On receipt of this, the journalist asked for further information on the liraglutide/obesity trial programme. The communications team asked her to email her enquiry and Novo Nordisk responded on 2 December with a non-promotional statement and cited top line phase 2 clinical trial results that were publicly available. In the particular situation, a timely response was required and therefore the liraglutide/obesity information was approved by two signatories on email, rather than going through the company's normal approval route. This was in line with the standard operating procedure for the provision of information to journalists. The above two documents were provided in accordance with the supplementary information to Clause 22.2; both were factual and balanced and were not given to the journalist for the purpose of encouraging members of the public to ask their doctor or other prescriber about Victoza. Having reviewed the Daily Mail article, Novo Nordisk saw no correlation between the information it reactively provided to the journalist and the article itself.

Novo Nordisk was alerted to the journalist's online and paper article entitled 'Jab that could help you drop two dress sizes in six months', via its media monitoring service on 27 December 2010. Having read the articles, on return from the Christmas holidays it sent a rebuttal to the journalist as the information in the article was factually incorrect and Novo Nordisk had been misquoted. Within this email correspondence (sent Tuesday, 11 January) Novo Nordisk also reminded the journalist that it would have appreciated sight of any quotations before publication so that it could ensure it was factually accurate and a fair representation of any comments provided.

Within the article itself, Novo Nordisk's managing director was quoted as stating 'We have had phenomenal results from the first clinical trials in obesity' and that effects were 'life-changing'. Novo Nordisk noted that this was not what was said, and it had been misquoted in the article.

Novo Nordisk stated that neither it nor, to the best of its knowledge, information and belief, any other member of the Novo Nordisk group of companies outside the UK, issued any company announcement, press release or any other communication, in relation to the Daily Mail articles.

Novo Nordisk explained that a professor, a leading expert in the field of obesity who was referred to in the Daily Mail article, was an investigator for the company in the phase 2 clinical trial programme investigating liraglutide for the treatment of obesity. It was also planned that he would be involved in the phase 3 trial programme. In addition, he had been involved in global Novo Nordisk advisory boards in relation to these trial programmes, but had not been trained by Novo Nordisk, nor had he been asked by Novo Nordisk to speak with the media.

Novo Nordisk stated that neither it nor, to the best of its knowledge, information and belief, any other member of the Novo Nordisk group of companies outside the UK, engaged with the professor to provide quotations to the journalist for the Daily Mail articles.

The firm objective of the meeting with the journalist was to raise the awareness of diabetes with a health correspondent, using the slide deck discussed during the meeting. Two further documents were provided to the journalist after the meeting in accordance with the supplementary information to Clause 22.2 of the Code. In summary, Novo Nordisk did not use the meeting, nor did it use the provision of further information to the journalist after the meeting, to promote liraglutide as a treatment for obesity. Furthermore, the managing director was misquoted in the article for which a rebuttal was sent to the journalist. Novo Nordisk also understood that the journalist had independently educated herself in this matter and it was not Novo Nordisk that had driven her interest in this subject. Novo Nordisk therefore did not believe it had breached Clauses 2, 9.1, 22.1 or 22.2 of the Code.

In response to a request for further information Novo Nordisk explained that in early September 2010, it briefed its agency to provide a proposal for a media programme to raise the profile of Novo Nordisk and strengthen its relationships with journalists. The agency emailed a draft proposal on 17 September 2010, a copy of which was provided, which put forward a wide range of potential topics for discussion, including Novo Nordisk's commitment to changing diabetes. The

communications team met the agency on 28 September to discuss its provisional proposal.

In the event Novo Nordisk decided that while its agency would handle the logistics for any such media meetings, Novo Nordisk's managing director would be briefed in-house by Novo Nordisk. This led to the certified slide deck which Novo Nordisk's managing director used for the basis of his meeting with the journalist. It was never discussed within Novo Nordisk or with its agency that the meeting with the journalist would cover liraglutide and obesity.

The invitation to the journalist to meet Novo Nordisk was sent by Novo Nordisk's agency; a copy was provided. The Daily Mail was selected to take part in the programme as it was a key stakeholder in consumer press. The journalist, the science correspondent, was targeted specifically because Novo Nordisk's analysis had suggested that she had a particularly strong interest in writing about diabetes. The meeting with the journalist lasted one hour fifteen minutes. The journalist was not provided with a copy of the Victoza summary of product characteristics (SPC). Novo Nordisk reiterated that the journalist's contact with the professor was not facilitated by Novo Nordisk or one of its agents.

PANEL RULING

The Panel noted that Clause 22.1 prohibited the advertising of prescription only medicines to the public. Clause 22.2 permitted information to be supplied directly or indirectly to the public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific product. Complaints about articles in the media were judged on the material provided by the company; such material should comply with the Code and in particular Clause 22.

The Panel noted that the complainant referred to an article published on 27 December 2010 in the Mail Online entitled 'Jab that could help you drop two dress sizes in six months'. Liraglutide was described as a diet drug that could be available in three years and as a jab that had produced phenomenal results. It was stated to be 'More than twice as good as anything on the market'. The article explained that liraglutide 'lowers blood pressure, raises "good" cholesterol and can prevent and even cure diabetes'. Its current use in diabetes was mentioned as was the ongoing trial programme in obese men and women. Comparative data with orlistat, a medicine licensed for weight loss, was discussed which appeared to have been taken from Astrup *et al* (2009) and which was provided to the Daily Mail journalist at her request. The Novo Nordisk managing director was quoted as stating 'We have had phenomenal results from the first clinical trials in obesity' and 'that the effects on confidence and health were life-changing'. The article also featured quotations from an academic expert in hormones and weight loss.

The Panel noted that Novo Nordisk's PR agency had developed a media programme designed to raise the profile of Novo Nordisk and strengthen its relationships with journalists. A series of meetings on varying topics had been arranged with individual journalists. In the Panel's view, the selection of such journalists should stand up to scrutiny; it might be unacceptable to select a journalist who had repeatedly published material related to the subject matter of a proposed meeting which was inconsistent with the Code. In its draft proposal for the media programme, Novo Nordisk's agent had listed as potential topics for discussion with the Daily Mail journalist, modern life with diabetes, how treatments were evolving to improve day-to-day lives of patients and the future of diabetes (pipeline).

The Panel noted that Novo Nordisk's agency had arranged a meeting with the journalist to discuss the human, social and financial impact of diabetes and Novo Nordisk's heritage with diabetes care. The presentation delivered at the meeting 'Changing the future of diabetes' discussed the incidence, human, social and economic consequences of diabetes. Slide 15 described the company's range of rapid-acting, long-acting and pre-mixed insulin although no brand names were mentioned. The following slide was headed 'GLP-1 receptor agonist': whilst not mentioning liraglutide by name it was described as a treatment for type 2 diabetes as an adjunct to diet and exercise in combination with specified anti-diabetic tablets. Slide 17 headed 'Addressing future diabetes care needs' listed 'Next generation insulin analogues', 'Incretin therapies', 'Oral insulin and oral GLP-1' and 'A cure for Type 1 diabetes'. None of the slides mentioned obesity. The presentation concluded by a discussion of work undertaken by Novo Nordisk to change diabetes through partnerships, access and quality of life. Slide 22 detailed Novo Nordisk's impact on six quality of life parameters for people with diabetes: the second bullet point read 'Only company with a once-daily GLP-1 analogue'. The Panel queried whether, given the stated aim of the meeting, the presentation had included disproportionate emphasis on liraglutide.

The Panel noted that the meeting notes detailed a general discussion but did not appear to cover the presentation. The Panel had no way of knowing precisely what was said about the slides.

The Panel noted that according to the meeting notes, the journalist explained that she knew a lot about liraglutide from the European Obesity Conference and had also written about it on publication of the recommendation from the National Institute for health and Clinical Excellence (NICE) [for its use in diabetes]. The journalist requested information on how liraglutide worked, its mode of action and trials for obesity and

timelines. The journalist was told she would be provided with a liraglutide backgrounder and published obesity trial results (Astrup *et al*). The journalist later asked about the timelines of getting liraglutide on the market for obesity and was told that a rough timeline might be three years. According to the meeting notes when the journalist referred to liraglutide and obesity the Novo Nordisk representatives steered the conversation back to the original topic. Although the Panel was concerned that liraglutide was the only specific medicine mentioned it did not appear from either the presentation slides or the meeting notes that the request about liraglutide and obesity was directly or indirectly solicited by Novo Nordisk.

The Panel had some concerns about the arrangements, presentation and discussion as set out above. Nonetheless the Panel did not consider that, on the evidence before it, the presentation, discussion and material provided to the journalist promoted a prescription only medicine to the public as alleged. No breach of Clause 22.1 was ruled. Nor, on balance, did the Panel consider that the material provided was not factual or balanced in relation to the licensed indication for liraglutide, nor did it otherwise encourage a member of the public to seek a prescription for it. Novo Nordisk did not proactively provide information on liraglutide and obesity. No breach of Clause 22.2 was ruled.

The Panel noted that the complainant had referred to Cases AUTH/2202/1/09 and AUTH/2234/5/09, wherein breaches of the Code had been ruled and additional sanctions imposed, as examples of Novo Nordisk's conduct in relation to the Code. The Panel noted that the cases cited concerned, *inter alia*, the pre-licence promotion of liraglutide and its promotion to the public. Turning to the present case, Case AUTH/2382/1/11, the Panel noted its rulings of no breach of the Code above and thus ruled no breach of Clause 9.1 and consequently, Clause 2.

Complaint received **19 January 2011**

Case completed **15 April 2011**

CASE AUTH/2385/2/11

BAXTER v NOVO NORDISK

NovoSeven leavepiece

Baxter complained about the source data used in support of a cost effectiveness claim which appeared in a NovoSeven leavepiece issued by Novo Nordisk. Baxter supplied FEIBA (factor viii inhibitor bypassing activity).

Baxter was concerned about the efficacy assumptions which fed into the supporting reference (Knight *et al* 2003) which described an economic model of the different strategies that could be used to treat episodes of bleeding in haemophilia patients with inhibitors. Baxter noted that the NovoSeven efficacy data (92%) fed into Knight *et al* 2003 was from Key *et al* (1998) and the efficacy input into the economic model for FEIBA (79%) was from a 1990 publication. Baxter alleged that Knight *et al* (2003) was out-of-date and did not reflect the efficacy of NovoSeven in clinical practice. In particular Baxter noted two more recent comparative studies (Astermark *et al* 2007 and Young *et al* 2008) failed to show a significant difference between NovoSeven and FEIBA.

Baxter submitted that a cost effectiveness claim should be based on current prices and the most up-to-date efficacy data of the products being compared.

The detailed response from Novo Nordisk is given below.

The Panel noted that the page of the leavepiece at issue was headed 'How can NovoSeven help you cut costs?' and immediately below was the claim 'A systematic review based on 2001 prices found that on-demand treatment with NovoSeven was cost-effective compared to treatment with pd-aPCC' referenced to Knight *et al* (2003). This was followed by the claim 'Now even better value' above text and an accompanying graph which illustrated a 30% increase (FEIBA) and a 5% decrease (NovoSeven) in prices since 2001.

The Panel noted that by means of a literature review Knight *et al* (2003) examined the cost-effectiveness of different strategies in the treatment of high-responding haemophilia A patients with inhibitors. The results showed that NovoSeven was the most cost-effective treatment for such patients, on demand or when they bled, compared with treatment with FEIBA. The reason why NovoSeven was the cheapest option despite its higher acquisition cost was due to the difference in success rates of treating minor bleeds at home, 92% for NovoSeven vs 79% for FEIBA. This reduced the need for further treatment doses and hospitalisation costs. The authors noted that the robustness of the assumptions needed further research.

The Panel noted that the cost-effective claim in the leavepiece was, in effect, based on an indirect comparison of NovoSeven and FEIBA in which the reported efficacy of the two products was 92% and 79% respectively. The source data were over 10 years old. Two more recent comparisons of NovoSeven and FEIBA (Astermark *et al* and Young *et al*) had suggested that the difference between the two was not so pronounced. A Cochrane review of 2010 (available when the leavepiece was produced) however, noted methodological flaws in these studies and that neither was able to prove the superiority of one treatment over the other. In a meta-analysis of the published efficacy data for NovoSeven and FEIBA, Treur *et al* (2009) noted 'that a typical regimen of NovoSeven is likely to produce significantly higher efficacy levels than typical FEIBA treatment at the 12, 24 and 36 hour time points'. A review of 18 studies by Knight *et al* (2009) stated that overall, higher efficacy and bleed cessation rates were noted for NovoSeven rather than FEIBA. The authors concluded that the wide variations in definitions of efficacy and study methods made comparison of results across studies difficult. Further head-to-head trials should incorporate a standardized measurement for defining efficacy. The Panel thus considered that the claim at issue was not a fair reflection of the totality of the evidence and was thus misleading. A breach of the Code was ruled.

Upon appeal by Novo Nordisk the Appeal Board considered that it had to decide whether the results of Knight *et al* (2003), to which the claim at issue was referenced, were robust enough to be relied upon in 2011.

The Appeal Board noted that a systematic review of the relevant literature by Knight *et al* (2009) noted the paucity of comparative studies, with only two direct head-to-head trials (Astermark *et al* and Young *et al*). The authors stated that although, overall, the published literature reported higher efficacy for NovoSeven (81-91%) than for FEIBA (64-80%), the measurement of efficacy of the two was open to interpretation due to a wide variety of methods being used to evaluate effectiveness. It was recommended that further head-to-head, randomised, controlled trials should incorporate a validated standard method of efficacy assessment. In that regard the Appeal Board noted, for instance, that the efficacy results from Key *et al* had been reported at 3 hours (92% for NovoSeven) whereas the Treur *et al* meta-analysis reported efficacy at 12, 24 and 36 hours (66%, 88% and 95% respectively for NovoSeven and 39%, 62% and 76% for FEIBA).

The Appeal Board noted that although most of the published data consistently reported higher efficacy

for NovoSeven than FEIBA, neither of the two direct comparisons as noted by the Cochrane report, were able to prove superiority of one over the other. Treur *et al* stated that their analysis suggested that NovoSeven was more effective than FEIBA; Knight *et al* (2009) stated that future trials should incorporate a validated standard method of efficacy assessment and the Cochrane report stated that there was a need for further well-designed, adequately powered, randomized controlled trials.

The Appeal Board noted that haemophilia with inhibitors was an ultra-orphan disease. Patient numbers were extremely limited and so it was difficult to design robust, comparative clinical studies. Nonetheless, reliable cost-efficacy modelling depended upon the input of robust data. In the Appeal Board's view the economic model derived by Knight *et al* (2003) did not accurately reflect all of the current evidence and the widely acknowledged limitations on the data. The Appeal Board upheld the Panel's rulings of a breach of the Code.

Baxter Healthcare Ltd complained about a leavepiece (ref UK/NV7/0809/0125a) for NovoSeven (eptacog alfa (activated)) produced by Novo Nordisk Ltd. NovoSeven was indicated, *inter alia*, to treat episodes of bleeding in haemophilia patients with inhibitors. The leavepiece was entitled 'Delivering rapid bleeding control to patients. Securing value for you'. The page at issue was headed 'How can NovoSeven help you cut costs?'. Baxter supplied FEIBA (factor viii inhibitor bypassing activity). Inter-company dialogue had failed to resolve the matter.

COMPLAINT

Baxter complained about the misleading use of data which reported 92% efficacy of NovoSeven in support of a cost-effectiveness claim. The supporting reference for the claims in the leavepiece, under the heading 'How can NovoSeven help you cut costs?' was Knight *et al* (2003) which described an economic model of the different strategies that could be used to treat bleeding episodes in haemophilia patients with inhibitors, using a Markov decision process. Baxter was concerned about the efficacy assumptions which fed into the model and thus allowed unreasonable claims to be made for the cost of treatment with NovoSeven.

Knight *et al* (2003) cited two previous economic analyses of the use of NovoSeven compared to FEIBA (Odeyemi and Guest 2002a and b), however, all of these publications derived their measure of the efficacy of NovoSeven (2003) (92%) from Key *et al* (1998). By contrast the efficacy rate input into the model by Knight *et al* (2003) for FEIBA was 79% for home treatment derived from Hilgartner *et al* (1990).

Baxter alleged that the use of Knight *et al* (2003) as a measure of efficacy for the health economic assessment of NovoSeven was misleading, and did not promote NovoSeven objectively. This reference was out-of-date and did not reflect the efficacy of NovoSeven in clinical practice.

Baxter noted that two more recent and robust publications directly compared the two products in objective terms. The first, Astermark *et al* (2007), was a randomised, comparative, cross-over study of the two products where each subject served as their own control. Although the primary endpoint of the study to show equivalence was not met, rates of efficacy for the two products were similar at all time points.

The second, Young *et al* (2008), was also a randomised comparison. There were two different dose regimes used for NovoSeven in this study; in terms of pain and mobility (the primary end points) no statistically significant differences were seen between the two products.

Baxter noted that in 2010 the Cochrane Collaboration published a systematic review of bypassing agents. Only Astermark *et al* and Young *et al* met the review criteria in terms of design and quality and were thus included in the formal analysis. Although a formal meta-analysis could not be carried out due to the difficulty of comparing the two studies, the authors concluded that the trials 'did not show superiority of one treatment over the other'.

The cost comparisons made in the leavepiece were based solely on the measures of efficacy used by Knight *et al* (2003) and derived from Key *et al*. Each of the economic analyses had shown NovoSeven to be cheaper than FEIBA in routine use; however this was primarily driven by the disparate efficacy measures used which did not reflect current comparative data, clinical practice or experience. Novo Nordisk updated these economic models with recent prices; however the underlying efficacy assumptions were unchanged.

Baxter noted that Key *et al* was the subject of a warning letter sent to Novo Nordisk by the US Food & Drug Authorisation (FDA) in 2004. The FDA believed the article was substantially flawed and was not robust enough to serve as the basis for promotional claims for NovoSeven, either for safety or efficacy. In particular, the FDA's concerns related to patient enrolment, treatment and monitoring.

Baxter argued that, to be fair, a cost-effectiveness claim should be based on current prices and the most up-to-date efficacy data for the products being compared. On the basis that the efficacy data used by Novo Nordisk was from a single arm study from 1998, when there were good quality randomised comparative studies from 2007 and 2008, Baxter believed that Novo Nordisk had been very selective in its use of evidence to support its claims. This was not balanced, it was misleading and in breach of the Code.

Baxter believed that the promotion of NovoSeven as a less expensive option than FEIBA in this patient

group, and the promotional use of studies based on this specific efficacy claim were both misleading, in breach of Clause 7.3.

Baxter had noted that it had unsuccessfully asked Novo Nordisk to stop using these references in its promotional materials.

RESPONSE

Novo Nordisk stated that the leavepiece was produced for the NovoSeven key account managers to use to highlight the importance of rapid bleed control in haemophilia patients with inhibitors. Furthermore, the leavepiece highlighted the costs of treatment and cost effectiveness of NovoSeven in the home treatment setting as the first line of management of mild to moderate bleeds in these patients. Following Baxter's initial complaint, the item was withdrawn from circulation on 8 November 2010.

Efficacy assumptions in cost-effectiveness modelling

Novo Nordisk ascertained from Baxter's complaint and from inter-company dialogue, that its main concern was the alleged misleading use of Key *et al*, which reported 92% efficacy for NovoSeven, as the primary source of efficacy data for NovoSeven for cost effectiveness analyses. Baxter claimed this was communicated in its letters to Novo Nordisk, dated 22 October and 22 November 2010. Novo Nordisk noted that neither of these letters included information or any criticism of the use of this reference to support the efficacy of NovoSeven. This was first highlighted when Novo Nordisk asked Baxter to provide an agenda for a teleconference that Baxter requested as part of inter-company dialogue.

Baxter claimed its complaint related a page of the leavepiece which referred to the economic model published by Knight *et al* (2003). This study concluded that on-demand treatment with NovoSeven was cost effective compared with treatment with FEIBA. Novo Nordisk noted that Knight *et al* (2003) was undertaken by the School of Health and Related Research (ScHARR), University of Sheffield, which received funding for the study from the Department of Health. Furthermore, the economic analysis was developed with the input of clinical expert advice and was reviewed by a representative from the National Institute for health and Clinical Excellence (NICE).

Baxter alleged that the efficacy assumption, based on Key *et al*, that fed into the economic model published by Knight *et al* (2003) allowed unreasonable claims to be made for the cost of treatment with NovoSeven. Hence, Baxter believed the use of the Key *et al* as a measure of efficacy for the health economic assessment was misleading and did not promote NovoSeven objectively.

Justification for use of Key *et al*

Novo Nordisk stated that Knight *et al* (2003) used the results of a systematic review of the economic literature to inform the development of the economic model, with particular reference to the economic models published by Odeyemi and Guest (2002a and b) and Colowick *et al* (2000).

Clinical effectiveness rates for NovoSeven and FEIBA were taken from Odeyemi and Guest (2002a and b). Knight *et al* (2003) stated that the selection of these clinical studies was supported by the results of a clinical effectiveness review reported by Lloyd Jones *et al* (2003).

Cross referencing to the Odeyemi and Guest references, the following justification was given for the selection of Key *et al*: 'This was selected as the basis of the efficacy data following a literature review and was endorsed by the expert panel involved in the development of this analysis'.

These three economic evaluations (Knight *et al* 2003, Odeyemi and Guest 2002a and b) were peer reviewed published studies that used Key *et al* as the source of NovoSeven efficacy data. The use of this study was also validated by expert clinical opinion and was supported by the results of Lloyd Jones *et al*. As a result, Novo Nordisk had no reason to question the validity of using these data as the source of efficacy data for NovoSeven in this analysis. Furthermore, the economic evaluation undertaken by Knight *et al* (2003) included extensive sensitivity analyses which showed that the efficacy of NovoSeven would need to be reduced from 92% to <84% in order for FEIBA to become cheaper.

Astermark *et al* and Young *et al*

Baxter provided evidence from two comparative studies (Astermark *et al* and Young *et al*) that were published after Knight *et al* (2003). These studies had been subject to a systematic review by the Cochrane Collaboration in 2010. This review compared the results of comparative studies only, of which there were two available, and concluded that the trials did not show superiority of one treatment over the other.

The FENOC study (Astermark *et al*) was a prospective, open-labelled, cross-over, clinical equivalency study. The authors acknowledged that the study lacked statistical power and the primary end point for equivalency at the 6 hour interval was not achieved. Furthermore, in a pre-determined definition of therapeutic equivalence in the study, the two products were not equivalent at any stage of the designated post-infusion time points in a study not powered for superiority.

Baxter proposed that in Young *et al*, there was no statistically significant difference between the two products. However, Baxter had omitted important contextual information about this citation. The

efficacy evaluations in this trial included two methods:

- A subjective global treatment response algorithm for pain assessment and mobility at specific time points (which was not a validated method assessment). Baxter had correctly highlighted that there were no statistically significant differences between NovoSeven and FEIBA and this related only to this pain and mobility assessment.

- The percentage of patients achieving bleed resolution without needing rescue medication within 9 hours of the first administration of the trial product. Novo Nordisk stressed that this efficacy evaluation was more relevant for a health-economic evaluation than the global treatment response algorithm. In this evaluation, the percentage of patients who required additional rescue medication was significantly lower for the NovoSeven 270mcg/kg dose group vs FEIBA (p=0.032) and approached significance (p=0.069) in the multiple dose group (90mcg/kg x 3 doses) vs FEIBA. The efficacy of both NovoSeven treated groups (91.7% efficacy for the NovoSeven 270mcg/kg group and 90.8 % efficacy for the 3 x 90mcg/kg) in this randomised setting were consistent with the efficacy evaluation in the real world clinical practice in Key *et al*.

Ideally there should be a systematic approach to identifying all the relevant data for use in an economic evaluation and Novo Nordisk pointed out the limitations of conducting economic evaluations for rare diseases, where it was recognised that the data were more limited.

Literature reviews

Since the economic evaluation by Knight *et al*, there had been three further systematic reviews of the clinical literature (Cochrane review, Knight *et al* (2009) and Treur *et al*).

- Novo Nordisk accepted the Cochrane review concluded that on the basis of the comparative evidence the two published trials did not demonstrate superiority of one product over another. Once again, however Novo Nordisk noted that the inclusion criteria for this review only included comparative trials. Again, Baxter had omitted important contextual information as stated in the conclusion of the Cochrane review. This Cochrane review concluded that more advanced methodologies were required to address the problem of high heterogeneity between studies. The review referred to the Bayesian meta-analysis published by Treur *et al* and concluded that other systematic reviews might help in the choice of the more effective concentrates, by using a Bayesian approach to pool randomised and non randomised evidence.

- Knight *et al* (2009) included data from such trials and concluded that estimates of efficacy from randomised clinical trials using dosing regimes in line with the guidelines were higher for NovoSeven (81-91%) than for FEIBA (64-80%).

- Treur *et al* included data from all published studies using a Bayesian meta-regression and concluded a typical NovoSeven regimen would resolve joint bleeds more effectively than a typical FEIBA regimen. This demonstrated that a typical regimen of NovoSeven (90mcg/kg repeated every 3 hours as necessary) resulted in cumulative bleed resolution of 66%, 88% and 95% after 12, 24 and 36 hours respectively. This compared with 39%, 62% and 76% for a typical FEIBA regimen (75IU/kg repeated every 12 hours if necessary). As far as Novo Nordisk was aware Treur *et al* was the only meta-analysis that combined all of the available clinical evidence for NovoSeven and FEIBA. These figures were statistically significant and also robust in sensitivity analyses. The meta-analysis integrated data from over 2000 joint bleeds and provided more relevant information on treatment efficacy than the results of individual studies. In order to assess the impact of individual studies on the results of the meta-analysis sensitivity analyses were undertaken. When the two direct comparator trials were weighted more heavily in the analysis (Astermark *et al* and Young *et al*), NovoSeven treatment remained significantly more effective than FEIBA.

On this basis, Novo Nordisk believed the efficacy assumptions used in the Knight *et al* (2003) economic model (92% in Key *et al* and 79% in Hilgartner *et al* 1990) appeared to be consistent with the evidence obtained from the available systematic reviews and meta-analysis.

Baxter referred to Novo Nordisk continuing to update these economic models with recent prices. This was in fact presented on a further page of the brochure. Novo Nordisk appreciated that this did not include adequate detail on the assumptions used for the economic evaluation and this had already been resolved with Baxter as part of the inter-company dialogue. Novo Nordisk noted that this economic analysis was intended to update the economic evaluation published by Knight *et al* (2003) to assess the impact of changes in treatment cost since 2001, when the analysis was undertaken. Updating the efficacy data used in the analysis would not permit a comparison with 2001 values. However based on the evidence presented above Novo Nordisk contended that the efficacy assumptions used in the economic evaluation were consistent with the current evidence.

FDA warning letter (2004) issued to Novo Nordisk in USA

Baxter also referred to an FDA warning letter sent to Novo Nordisk about the use of Key *et al* in a Spanish language promotional brochure for use in the US. The letter noted that Key *et al* was a home treatment study which reported that 92% of bleeds

were resolved within 24 hours, with a mean 2.3 doses of NovoSeven, administered at a mean of 1.2 hours from the start of the bleed. The FDA concluded that the design of the study did not allow a determination of safety and efficacy for the purpose of product labelling and should therefore not be used to support these specific promotional claims in the US as per guidance of a specific clause of the FDA. Novo Nordisk maintained that this related to a very specific promotional issue in the US, which was not relevant in this case. Nevertheless, the efficacy of 92% of bleed resolution in a specific time frame was consistent with recently published data as demonstrated above.

Conclusion

In the concluding two paragraphs of its complaint, Baxter alleged that it believed the promotion of NovoSeven as a less expensive option than FEIBA in this patient group was misleading in breach of Clause 7.3. Baxter concluded by stating that to be fair, a cost effectiveness claim should be based on current prices and the most up to date efficacy data for the products being compared. Novo Nordisk agreed and maintained that the cost effectiveness evidence was consistent with the efficacy data in the published literature for both of these products. Key *et al* remained a seminal paper for NovoSeven and the results of subsequent systematic reviews and meta-analysis supported the assumption of 92% efficacy for NovoSeven. Economic evaluations inevitably required the modelling of cost and efficacy assumptions from a number of disparate sources which had the potential to generate uncertainty in the results. This emphasised the importance of extensive sensitivity analyses to assess the robustness of the model results. The economic evaluation undertaken by Knight *et al* (2003) showed that the efficacy of NovoSeven would need be reduced from 92% to <84% in order for FEIBA to become cheaper.

Based on this evidence Novo Nordisk denied that use of this efficacy assumption for cost effectiveness evaluations was misleading and refuted a breach of Clause 7.3.

PANEL RULING

The Panel noted that the page of the leavepiece at issue was headed 'How can NovoSeven help you cut costs?' and immediately below was the claim 'A systematic review based on 2001 prices found that on-demand treatment with NovoSeven was cost-effective compared to treatment with pd-aPCC' referenced to Knight *et al* (2003). This was followed by the claim 'Now even better value' above text and an accompanying graph which illustrated a 30% increase (FEIBA) and a 5% decrease (NovoSeven) in prices since 2001.

The Panel noted that by means of a literature review Knight *et al* (2003) examined the cost-effectiveness of different strategies in the treatment of high-responding haemophilia A patients with inhibitors. The results showed that NovoSeven was the most cost-effective treatment for such patients, on demand or when they bled compared with treatment with FEIBA. The authors noted that the reason why NovoSeven was the cheapest option despite its higher acquisition cost was due to the difference in success rates of treating minor bleeds at home, 92% for NovoSeven (Key *et al*) vs 79% for FEIBA (Hilgartner *et al*). This reduced the need for further treatment doses and hospitalisation costs. The authors also noted that the robustness of the assumptions needed further research.

The Panel noted each party's submission on Key *et al*. The Panel noted that haemostasis was achieved in 92% of evaluable bleeds with NovoSeven. In the intention to treat analysis of all bleed events the authors stated that efficacy outcomes were equivalent to the evaluable bleeds, with an effective response in 88% of treated episodes.

The Panel noted Novo Nordisk's submission that Knight *et al* (2003) had stated that the selection of the studies by Odeyemi and Guest was supported by the results of a clinical effectiveness reviewed reported by Lloyd Jones *et al*. The Panel further noted that Lloyd Jones *et al* was the same group as Knight *et al* (2003).

Astermark *et al* was a prospective, open-label, randomized study designed to test equivalence of FEIBA and NovoSeven in certain joint bleeds. The primary outcome was evaluation 6 hours after treatment. The criterion for declaring the products' equivalence at 6 hours by patient report was not met. The products were equivalent in terms of bleeding cessation at 24 hours; NovoSeven 85.7%, FEIBA 90.5%, p=0.038; and at 48 hours, NovoSeven 92.7% and FEIBA 95.1%, p=0.001. The study authors noted that failure to achieve equivalence, particularly at the 6 hour time point, was probably related to a lack of statistical power. It could not be construed as evidence that one product was different or better. The study authors also noted that in exploratory analysis neither product was superior to the other either in terms of efficacy or ability to stop bleeding at any time point. The study concluded that the products 'appeared to exhibit a similar effect on joint bleeds although the efficacy between the products was rated differently by a substantial proportion of patients'.

Young *et al* evaluated the efficacy and safety of single 270mcg/kg dose NovoSeven vs standard 90mcg/kg dose NovoSeven and FEIBA for controlling joint bleeds in a home treatment setting. Efficacy was assessed by the requirement for additional haemostatics within 9 hours and a novel global response algorithm. The percentage of patients requiring additional haemostatic medication was significantly greater for the FEIBA treatment group than for the single dose 270mcg/kg NovoSeven group. The efficacy difference between the FEIBA and the NovoSeven 3 x 90mcg/kg group approached but did not achieve statistical

significance (p=0.069). No significant differences in treatment for the global response algorithm were discovered although a trend towards a better response with NovoSeven was noted.

The Panel noted that efficacy was rated by the patient in both Young *et al* and Astermark *et al*.

The Panel noted that the leavepiece at issue was dated August 2010. The Cochrane Collaboration report was last assessed as up-to-date on 6 July 2010. It thus appeared that it was available when the leavepiece was produced and used. The Cochrane report stated that Young *et al* and Astermark *et al* qualified for inclusion but the data were not presented in such a way as to allow these to be combined in a meta-analysis. Each study showed methodological flaws and neither was able to prove the superiority of one treatment over the other. The authors stated that based on the available randomized evidence it was not possible to consider one treatment more efficacious or safer than the other. The authors' separate analysis of Young *et al* and Astermark *et al* showed that NovoSeven and FEIBA were, *inter alia*, similar in efficacy. The authors noted that non-randomized evidence could usefully be taken into account and referred to Treur *et al*.

Treur *et al* was also a meta-regression analysis of the published efficacy data of NovoSeven and FEIBA. Seventeen studies were included including Astermark *et al*, Key *et al* and Young *et al*. Pooled efficacy levels for typical NovoSeven and FEIBA regimens were estimated. At 12 hours the efficacy was 66% (NovoSeven) and 39% (FEIBA), at 24 hours 88% NovoSeven and 62% (FEIBA) and at 36 hours 95% (NovoSeven) and 79% FEIBA. The study authors noted that the results suggested 'that a typical regimen of NovoSeven is likely to produce significantly higher efficacy levels than typical FEIBA treatment at the 12, 24 and 36 hour time points'. It was noted that the models' assumption that second or subsequent doses had similar efficacy was arguably unrealistic. However, data for more relevant parameters was not available. Many limitations were discussed including hierarchy of study designs, relevance of outcome data and bleeding sites.

Knight *et al* (2009) reviewed 18 studies to establish, *inter alia*, robust estimates of efficacy and speed of bleed resolution. Overall, whilst noting that comparisons between studies were difficult, the overall efficacy rates from randomized clinical trials were 64-80% for FEIBA and 81-91% for NovoSeven 12 hours after treatment. In the non-randomized trials 65-88% for FEIBA and 90% for NovoSeven treatment. Overall higher efficacy and bleed cessation rates were noted for NovoSeven rather than FEIBA. The authors concluded that the wide variations in definitions of efficacy and study methods make comparison of results across studies difficult. Further head-to-head trials should incorporate a standardized measurement for defining efficacy.

The Panel noted that the cost-effective claim in the leavepiece was, in effect, based on an indirect comparison of NovoSeven and FEIBA in which the reported efficacy of the two products was 92% (Key *et al*) and 79% (Hilgartner *et al*) respectively. The source data were over 10 years old. Two more recent, direct comparisons of the NovoSeven and FEIBA had suggested that the difference between the two was not so pronounced. A Cochrane review of 2010 stated that the trials (Astermark *et al* and Young *et al*) did not show a difference in the effectiveness of the two products. The review by Knight *et al* (2009) referred to the difficulties in comparing data across studies. The Panel thus considered that the claim at issue was not a fair reflection of the totality of the evidence and was thus misleading. A breach of Clause 7.3 was ruled.

During its consideration of this case, the Panel noted that the page of the detail aid at issue featured a graph which showed the percentage price change for FEIBA and NovoSeven in the period 2001 to 2010. In that time the cost of FEIBA had risen by 30% whilst the cost of NovoSeven had decreased by 5%. The graph appeared to show that NovoSeven was 35% less expensive than FEIBA. The Panel was concerned that showing the percentage change in price might give a misleading impression of the absolute differences in acquisition cost and asked that Novo Nordisk be advised of its concerns in this regard.

APPEAL BY NOVO NORDISK

Novo Nordisk stated that the leavepiece highlighted the importance of rapid bleeding control in haemophilia patients with inhibitors and the cost effectiveness of NovoSeven in the home treatment setting in the first line management of mild to moderate bleeds.

Background to complaint

Novo Nordisk submitted that Knight *et al* (2003) demonstrated the cost effectiveness of NovoSeven vs FEIBA from an NHS perspective using a modelled economic evaluation. Modelled economic evaluations aimed to determine the cost effectiveness of one product over another and were based on a synthesis of the best available evidence at the time and most plausible assumptions that reflected clinical practice. The robustness of the results based on these assumptions was tested using sensitivity analyses, where one or more of the model inputs were altered and the impact on the results assessed. The sensitivity analysis performed on the economic evaluation undertaken by Knight *et al* (2003) showed that the efficacy of NovoSeven would need to be reduced from 92% to less than 84% in order for FEIBA to become cheaper or the efficacy of FEIBA increased from 79% to more than 88%. This demonstrated that the results of Knight *et al* (2003) were robust to changes in the model inputs and NovoSeven remained cost effective compared with FEIBA (table 14 of Knight *et al* 2003).

Novo Nordisk noted that haemophilia with inhibitors was an ultra-orphan disease and it was well recognised that data were more limited than for more common conditions. Over the last 30 years a number of studies for both NovoSeven and FEIBA had been published including two comparative, randomised, controlled trials (RCTs), and several uncontrolled and single arm studies. The Panel had stated that two recent direct comparisons of NovoSeven and FEIBA (Astermark *et al* and Young *et al*) had suggested that the efficacy difference between the two products was not so pronounced as those included in the economic model by Knight *et al* (2003) and stated that these findings had been confirmed by the Cochrane report. In the clinical practice management of haemophilia with inhibitors, treatment regimens were based on individual patient's haemostatic profile and the need to stop bleeding effectively. Treatment was not based on rigid regimens in RCTs and to do so would be unrealistic. For a rare disease such as haemophilia with inhibitors, it was almost impossible to design a single study that would statistically demonstrate the superiority of one product over another as trials were limited by small patient numbers. In the UK, there were just 189 patients with haemophilia with an inhibitor, (UK Haemophilia Centre Doctors' Organisation - Annual Report 2010). In ultra-orphan diseases, it was relevant to consider all of the available evidence, from both RCTs and non RCTs and therefore a meta-analysis of this evidence was recommended to increase the sample size on which the efficacy was based. This was supported by the conclusions of the Cochrane report. The Treur *et al* meta-analysis best reflected the totality of all the clinical evidence, including the two head-to-head trials and the key single arm studies in terms of number of bleeds for both products (Key *et al* and Negrier *et al* 1997).

Novo Nordisk noted that the Panel had stated that the authors of the Cochrane report had noted that non-randomised evidence could usefully be taken into account and referred to Treur *et al*. Treur *et al* was a meta-regression analysis of the published efficacy data of NovoSeven and FEIBA from 1965 up to October 2007. Novo Nordisk noted that in one set of sensitivity analyses, the Treur model was re-estimated after removing, sequentially and then together, two large 'outlier' studies, Key *et al*, which reported on the efficacy of NovoSeven, and Negrier *et al*, which reported on the efficacy of FEIBA, in order to test whether either one or both of these studies could skew the overall efficacy results in either direction. Treur *et al* stated that despite these omissions, the modelled NovoSeven treatment remained significantly more efficacious than modelled FEIBA treatment at 12, 24 and 36 hours. The efficacy results at 36 hours were 95% for NovoSeven and 79% for FEIBA. These were consistent with the efficacy inputs used in Knight *et al* for NovoSeven (92%) and FEIBA (79-88%).

Novo Nordisk noted that the Treur *et al* meta-analysis had systematically identified and meta-analysed all of the available evidence and therefore the results of the analysis reflected the totality of the available evidence. Although this analysis was not available when Knight *et al* (2003) was published the results of this analysis were consistent with the efficacy inputs used in Knight *et al* (2003). The table below summarised the efficacy inputs used in the model by Knight *et al* and the efficacy figures that had since been published for NovoSeven and FEIBA.

Summary of published efficacy rates for NovoSeven and FEIBA

		COCHRANE			
	Knight *et al* (2003)	Young *et al* (both measured at 9 hours)	Astermark *et al* (Primary endpoint measured at 6 hours)	Knight *et al* (2009) (Systematic Review)	Treur *et al* + (efficacy modelled inputs measured at 24 and 36 hours) (meta-analysis)
NovoSeven	92% within 3-6 hours	91%	79%	81% - 91% (efficacy measured at 9 hours)	24 hours: 88% 36 hours: 95%
FEIBA	79% within 36 hours	63%	80%	64% - 80% (efficacy measured at 24 hours)	24 hours: 62% 36 hours: 76%

Based on this information Novo Nordisk disagreed with the Panel that the efficacy inputs for the analysis in Knight *et al* did not reflect the totality of the evidence and it maintained that these inputs were consistent with recently published evidence reflective of clinical practice.

Knight *et al* (2003) was an independent economic evaluation and when it was published it considered all of the available evidence. Although new clinical evidence had been published, there had been no new economic evidence for the UK to confirm or refute the conclusions, hence Knight *et al* (2003) remained the most recent publication to compare the cost effectiveness of NovoSeven and FEIBA.

In conclusion Novo Nordisk submitted that the previously submitted evidence supported its claim 'How NovoSeven can help you cut costs' and reflected the totality of evidence in a rare disease area, as the efficacy differences were supported by the results of a recent meta-analysis and were therefore not misleading. The Panel had unfairly focussed on rigid RCT evidence in its ruling and erroneously omitted important contextual information regarding Treur *et al*.

COMMENTS FROM BAXTER

Baxter stated that modelled economic evaluations of medicines in clinical practice must be based on robust data. It was clear that Novo Nordisk had been highly selective in its choice of data sources for the comparative efficacy of the two products, and therefore it did not represent the total body of evidence.

According to the NICE guide to the methods of technology appraisal 2008, the most reliable evidence about relative treatment effects was from experimental studies with high internal and external validity. The highest level of evidence was derived from randomised prospective studies, particularly head-to-head studies where comparative efficacy measures could be derived.

Baxter submitted that in its complaint, and in its dialogue with Novo Nordisk, it had repeatedly referred to the only independent, randomised, head-to-head comparison between the two products, namely the FENOC study by Astermark *et al*. This study was one of only two deemed suitable for scrutiny by a subsequent Cochrane review of the two treatments in this patient group. This was the only valid source of comparative efficacy data between the two products.

Although FENOC demonstrated substantial variations in response to treatment between patients, and even between different bleeding episodes in the same patient, what was not demonstrated after repeated data analysis was superiority of one treatment over the other. This conclusion was mirrored in the Cochrane publication.

Economic models put forward by Novo Nordisk repeatedly showed NovoSeven as cost-effective compared with FEIBA, however these models used older, less robust sources of efficacy data, and gave misleading results.

Following the publication of FENOC, Carlsson *et al* (2008) conducted a cost-utility analysis using the efficacy measures reported in the earlier publication. With a few exceptions this model showed that treatment with FEIBA gave a lower average cost per treatment episode than NovoSeven, contrary to all the economic models quoted by Novo Nordisk. Although this study used non-UK prices as part of the evaluation, these were still reflected the price differential in the UK.

Novo Nordisk placed a lot of emphasis on the analysis of literature by Truer *et al*, however there were a number of issues with this publication. The NICE guide stated that in the absence of valid RCT evidence, evidence from studies least open to bias would be considered. Truer *et al* was a Bayesian analysis combining results of 18 studies, 11 of which were observational in design without a control group. Two studies included fewer than 10 patients, which could be considered small even in this ultra-orphan disease. The studies differed in the way in which outcomes were measured, only joint bleeds were considered (compared to total number of bleeds), and they were subject to publication bias. Although sensitivity analysis was carried out the authors did not report the results of the model when only data from randomised, head-to-head studies was included. Bearing all this in mind, in the light of randomised, controlled evidence from FENOC, it was hard for Novo Nordisk to argue that this publication was not open to bias.

Baxter alleged that it was not its intention or objective to claim that FEIBA was either more effective, or more cost-effective, than NovoSeven. It was clear from the evidence from well-designed studies that both products had a role in treatment, and that neither was superior to the other. Baxter's challenge to the promotional claims made by Novo Nordisk rested on this point. Taking the conclusion of the Cochrane publication that the two products were similar in terms of safety and effectiveness, the acquisition cost of each treatment became the determining factor.

Baxter stated that current list prices were £780 per 1000 U for FEIBA and £525.20 for 1mg NovoSeven, comparable to the costs quoted by Carlsson *et al*. Taking the dose regimens from FENOC as the example, the acquisition cost of the two medicines (rounded to the nearest hole vial) for a typical 70kg adult would be approximately £4,680 for FEIBA (85 U/kg, one dose) and £6,827 for NovoSeven (90mcg/kg, two doses 2 hours apart).

This was in line with observational data collected in Italy and published by Gringeri *et al* (2003). This group observed treatment of 52 patients with haemophilia A and inhibitors over an 18-month period and recorded all costs related to their care, and various measures of quality of life. The average monthly cost of care was just under €18,000 per patient; NovoSeven represented approximately half of this cost. Although approximately half the NovoSeven was used to cover surgical procedures, even allowing for this it was illuminating to note the relative contributions to overall treatment costs of FEIBA and NovoSeven in this publication.

Baxter submitted that it was well known that recombinant therapies were expensive – given the widely accepted view that the two products were comparable in terms of efficacy, it was counter-intuitive for Novo Nordisk to claim superior cost-effectiveness for its product. As Novo Nordisk had admitted, the 92% efficacy figure for NovoSeven as used in its economic analysis was derived from Key *et al*. With regard to the appropriateness of this as a source of evidence, Baxter noted that it had been challenged by the FDA as being insufficiently robust as a basis for safety or efficacy claims and, additionally, it reported treatment of patients outside the licensed indication for FEIBA, and reported unlicensed doses of NovoSeven.

Baxter alleged that given that no sub-analysis of the results in haemophilia A patients could be done in this study, it was impossible to establish the true efficacy of NovoSeven in this report. Further, as the exclusion criteria made clear, it was very likely that patients who failed to respond to NovoSeven were not included in the final efficacy analysis, further skewing the results.

As the Panel had noted in its ruling, the claim in question was based on selective use of data, it did not fairly reflect all the evidence and was thus misleading. The appeal by Novo Nordisk had not

changed this, and Baxter was confident that the Panel's ruling was correct.

APPEAL BOARD RULING

The Appeal Board noted Novo Nordisk's submission at the appeal, that the leavepiece was to be used by representatives to open a discussion with prescribers about the cost effectiveness of using NovoSeven. The intention was to convince prescribers that NovoSeven was more cost effective than FEIBA.

The Appeal Board noted that although NovoSeven could be used to treat any episode of bleeding, the efficacy data from Key *et al*, which fed into the economic model of Knight *et al* (2003), related only to its use in mild to moderate episodes. The limitation of the data in this regard was not stated on the page in question. The following page of the leavepiece (overleaf) featured a graph headed 'Cost of managing a mild-to-moderate bleeding episode based on current prices' which was the first mention of 'mild to moderate' in the leavepiece in question.

The Appeal Board considered that it had to decide whether the results of Knight *et al* (2003), to which the claim at issue was referenced, were robust enough to be relied upon in 2011. The Appeal Board noted that a systematic review of the relevant literature by Knight *et al* (2009) (6 randomised controlled trials, 11 prospective or retrospective cohort studies and 1 meta-analysis) noted the paucity of comparative studies with only two direct head-to-head trials (Astermark *et al* and Young *et al*). The authors stated that although, overall, the published literature reported higher efficacy for NovoSeven (81-91%) than for FEIBA (64-80%), the measurement of efficacy of the two was open to interpretation due to a wide variety of methods being used to evaluate effectiveness. It was recommended that further head-to-head, randomised, controlled trials should incorporate a validated standard method of efficacy assessment. In that regard the Appeal Board noted, for instance, that the efficacy results from Key *et al* had been reported at 3 hours (92% for NovoSeven) whereas the Treur *et al* meta-analysis reported efficacy at 12, 24 and 36 hours (66%, 88% and 95% respectively for NovoSeven and 39%, 62% and 76% for FEIBA).

The Appeal Board noted that although most of the published data consistently reported higher efficacy for NovoSeven than FEIBA, neither of the two direct comparisons as noted by the Cochrane report, were able to prove superiority of one over the other. Treur *et al* stated that their analysis *suggested* that NovoSeven was more effective than FEIBA; Knight *et al* (2009) stated that future trials should incorporate a validated standard method of efficacy assessment and the Cochrane report stated that there was a need for further well-designed, adequately powered, randomized controlled trials.

The Appeal Board noted that haemophilia with inhibitors was an ultra-orphan disease. Patient numbers were extremely limited and so it was difficult to design robust, comparative clinical studies. Nonetheless, reliable cost-efficacy modelling depended upon the input of robust data. In the Appeal Board's view the economic model derived by Knight *et al* (2003) did not accurately reflect all of the current evidence and the widely acknowledged limitations on the data. The Appeal Board upheld the Panel's rulings of a breach of Clause 7.3. The appeal was thus unsuccessful.

Complaint received	**11 February 2011**
Case completed	**11 July 2011**

CASE AUTH/2389/2/11

ALLERGAN v ALCON

Promotion of Travatan

Allergan complained about a promotional campaign for Travatan (travaprost preserved with Polyquad) by Alcon which featured the picture of a vertical, long-stemmed rose with no thorns; thirteen thorns lay around the base of the stem. An advertisement featuring the image had appeared in the British Journal of Ophthalmology.

The detailed response from Alcon is given below.

Allergan submitted that the campaign visual was clearly a comparative image – implying that other products in the same therapeutic category, such as its product Lumigan (bimatoprost), had 'thorns' whilst Travatan had none. The clear implication was of an improved ocular safety profile and potentially a complete lack of ocular adverse events.

In inter-company dialogue, Alcon had submitted that the thornless rose was a comparative image, but only in as much as it was intended to represent a comparison with the original formulation of Travatan preserved with benzalkonium chloride (BAK).

Allergan knew of only one clinical study comparing Travatan preserved with Polyquad with Travatan preserved with BAK (Denis *et al* 2010) which demonstrated that the safety profile was similar for both products.

Allergan alleged that the visual was misleading in breach of the Code.

The Panel noted the picture of the thornless rose which ran down the left hand side of the advertisement. The prominent headline in the top right hand corner was 'Introducing BAK-free formulation Travatan'. In the Panel's view, most readers would associate the picture of the rose with the prominent headline and thus see the rose as representing Travatan without BAK.

The Panel considered that thorns on a rose stem would be seen as something injurious; the advertisement implied that Travatan preserved without BAK was free of such hazard.

The Panel noted that Travatan preserved with Polyquad was still associated with one of the ocular side-effects referred to in Section 4.4, Special warnings and precautions for use, of the summary of product characteristics (SPC) for Travatan preserved with BAK. Further, Section 4.8 of the SPC for Travatan preserved with Polyquad listed another ten possible ocular adverse events which were also listed as possible adverse events in the SPC for Travatan preserved with BAK. In this regard the Panel did not consider that the thornless rose was a fair reflection of the side effect profile of Travatan preserved with Polyquad compared with Travatan preserved with BAK. The advertisement was misleading and exaggerated the difference between the two. Breaches of the Code were ruled which were upheld on appeal. The Appeal Board, *inter alia*, noted the findings of Denis *et al* and considered that the visual was misleading and exaggerated the difference between the two formulations of Travatan as alleged.

The Panel did not consider that the thornless rose implied a potentially complete lack of side-effects as alleged; no breach of the Code was ruled.

The Panel did not consider that the visual in the advertisement implied any comparison with competitor products as alleged. No breach of the Code was ruled.

Allergan alleged that the claim 'Travatan BAK-free', used to alert customers to the newly formulated Travatan, misleadingly implied that the product was preservative-free, when in fact it was preserved with Polyquad. This preservative was clearly not 'side-effect free' as was generally implied in the advertisement and with the campaign visual. Allergan also considered the use of laboratory studies within the advertisement was unacceptable to support general claims regarding tolerability. Allergan was not aware of any clinical data to support the tolerability claims for Polyquad compared with BAK.

The Panel did not consider that the claims that Travatan was BAK-free implied that it was also preservative-free. The advertisement clearly referred to 'A multidose prostaglandin analogue with POLYQUAD'. The Panel did not consider that the claims were misleading as alleged. No breach of the Code was ruled.

The Panel noted that the advertisement included, *inter alia*, the claims 'Contains Polyquad, which had demonstrated a gentler effect on the ocular surface than BAK in laboratory studies' and 'Significantly less toxic to human conjunctive and coneal epithlial cells when compared to latanoprost solutions (preserved with 0.02% BAK *in vitro*)'. Both claims were referenced to animal or *in vitro* studies. The Code stated that care must be taken so as not to mislead with regard to the significance of such studies. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance significance.

The Panel considered that the animal and *in vitro* studies cited in the advertisement implied that BAK-free Travatan had a better safety profile compared with Travatan preserved with BAK. The only direct clinical comparison of the two (Denis *et al*) did not show that to be the case. The Panel considered that the advertisement was misleading and exaggerated in that regard. Breaches of the Code were ruled. High standards had not been maintained. A further breach of the Code was ruled. Alcon appealed these rulings.

The Appeal Board noted that under the heading 'Travatan BAK-free formulation:' the advertisement featured two bullet points which referred to animal and *in vitro* studies. In particular the claim 'Significantly less toxic to human conjunctive and corneal epithelial cells when compared to latanoprost solutions (preserved with 0.02% BAK *in vitro*)' was referenced to a study which compared the effects of Travatan BAK-free with travoprost and lantaprost which were both preserved with BAK on isolated human conjunctival epithelial cells. The Appeal Board noted that the authors stated that '…formulations preserved with Polyquad *might* be better for ocular surface health than solutions containing BAK' (emphasis added). In the Appeal Board's view 'Significantly less toxic…' as used in the advertisement was quite different to '…might be better…', as used in the study. The Appeal Board considered that in that regard the claim did not reflect the cited paper.

The Appeal Board considered that although the results of *in vitro* models might predict future clinical effects there was no guarantee that this would be so. When presenting animal and *in vitro* studies care was needed to ensure that, in the absence of clinical evidence, clinical effects were not inferred or claimed. The Appeal Board noted that the only clinical evidence available concluded that the safety profile of Travatan preserved with Polyquad was similar to that preserved with BAK.

The Appeal Board considered that the *in vitro* and animal data presented in the advertisement implied that BAK-free Travatan was better tolerated than that preserved with BAK and this was not supported by the available clinical data. The Appeal Board considered that the advertisement was misleading and exaggerated in that regard. The Appeal Board upheld the Panel's ruling on this point. The Appeal Board further considered that high standards had not been maintained and it upheld the Panel's ruling in this regard.

Allergan Limited complained about the promotion of Travatan (travaprost preserved with Polyquad) by Alcon Laboratories (UK) Limited. The complaint concerned a campaign which featured a picture of a vertical, single, long-stemmed rose in full bloom. Thirteen thorns lay around the base of the stem. An advertisement (ref TBF:AD:12/10:LHC) had appeared in the British Journal of Ophthalmology.

1 Campaign visual – A rose without thorns

COMPLAINT

Allergan noted that the Travatan campaign visual was a rose that had lost all of its thorns. The use of a rose without thorns was clearly a comparative image – implying that other products in the same therapeutic category, such as its product Lumigan (bimatoprost), had 'thorns' whilst Travatan had none. The clear implication was of an improved ocular safety profile and potentially a complete lack of ocular adverse events.

In inter-company dialogue Alcon had submitted that the rose without thorns was a comparative image, but only in as much as it was intended to represent a comparison with the original formulation of Travatan preserved with benzalkonium chloride (BAK). Allergan did not agree with this interpretation; even if this were the case there was a clear implication of an improved safety profile for Travatan preserved with Polyquad vs Travatan preserved with BAK. The implication of an improved safety profile vs the previous formulation was not supported by the clinical evidence.

Allergan knew of only one clinical study, published as an abstract and a poster, which compared Travatan preserved with Polyquad with Travatan preserved with BAK (Denis *et al* 2010). The study demonstrated that the safety profile was similar for both products. Indeed, the authors concluded that 'the safety profile of travoprost BAK free was similar to that of travoprost BAK'. The summary of product characteristics (SPC) for the BAK free formulation also listed eye irritation, dry eye, pruritus, eye pain and ocular discomfort as common undesirable effects.

Alcon had not supplied any additional clinical data which compared Travatan preserved with Polyquad and Travatan preserved with BAK to support the implication of an improved safety profile as illustrated by the visual.

Allergan alleged that the visual was misleading in breach of Clauses 7.2, 7.3 and 7.10.

RESPONSE

Alcon stated that it had reformulated Travatan by replacing the preservative BAK with Polyquad. Alcon no longer intended to market the BAK formulation of Travatan and therefore its promotional campaign raised awareness of the new formulation; the visual of a rose without thorns symbolised the difference between the old and new formulations of Travatan. The entire campaign was centred on this theme, and when the image was viewed in conjunction with the surrounding text there was no confusion as to the meaning. The material merely showed that Travatan was now BAK-free.

The decision to reformulate Travatan and replace BAK with Polyquad was based on extensive clinical and experimental data testifying to the particular risk of BAK causing eye irritation. BAK was the most widely used preservative in ophthalmic preparations for the treatment of glaucoma as it exhibited efficacious antimicrobial properties, yet its toxicity to the cornea and potential to damage the ocular surface had been well documented in the literature. In addition, a number of patients were allergic to BAK and confined to using single-dose preservative-free medicines. The particular problems associated with BAK, which were widely known within the ophthalmic community, were reflected in the special warning in Section 4.4 of the SPCs for all ophthalmic products containing BAK to the effect that BAK could cause punctate keratopathy and/or toxic ulcerative keratopathy. This warning was additional to the list of undesirable effects. The European Medicines Agency (EMA) did not require the inclusion of an equivalent special warning in the SPC or leaflet for the BAK-free version of Travatan. This clearly supported the position that BAK had a particular association with severe forms of eye irritation, whereas Polyquad, which had been used as a preservative in many ophthalmic formulations over the past 20 years or more, did not. Alcon believed that this testified to a real difference between the original and new formulations of Travatan. Indeed, the absence of BAK was an essential characteristic of the new formulation, and Alcon considered it appropriate and necessary to highlight this difference to ophthalmologists when promoting the new formulation of Travatan.

As the new formulation would completely replace the original formulation of Travatan, the purpose of the current marketing campaign was to announce and explain this important change to customers. The rose without thorns portrayed the difference between the original and new formulations and non-ambiguous accompanying text stated that Travatan was now BAK-free. The rose without thorns was a comparative image between the original formulation of Travatan and the new BAK-free formulation. The thorns represented the known ocular irritant, BAK. The new formulation of Travatan no longer contained BAK and therefore was 'thorn' free. This reflected the position in the SPC which showed that Travatan no longer contained BAK and the special warning in Section 4.4 of the SPC had been removed.

Alcon did not agree that the image, in its proper context, implied that the new formulation of Travatan had a complete lack of ocular adverse events or that overall it had an improved ocular safety profile. The visual (and the accompanying text) made it clear that the focus of the promotional material was to announce the removal of the particular irritant, BAK, from Travatan. In addition, the audience to whom the material was directed was well acquainted with glaucoma medicines and their side effects. Moreover, the safety profile of Travatan was unequivocally apparent from the prescribing information included in all materials and the SPC which was either available from the sales representative or via the electronic medicines compendium.

Alcon noted Allergan's reference to Denis *et al* in support of its allegation that the material was misleading and suggested that Travatan (BAK-free) had an improved ocular safety profile compared with Travatan preserved with BAK. However, as explained above, the rose without thorns image did not imply that overall Travatan had an improved ocular safety profile. Further, and in any event, Denis *et al* was a non-inferiority study and could therefore not have been expected to show the effects of long-term exposure to BAK. The particular problems with BAK were known to arise from chronic use; however Denis *et al* was only conducted over a period of three months and so could not have shown the effects of chronic use. Nevertheless, studies had shown that long-term use of BAK could be associated with undesirable adverse effects. It was also known that the use of BAK-free ophthalmic medicines could reverse previous ocular damage caused by BAK. Further to this, *in vivo* (animal) and *in vitro* cytotoxicity studies had shown that Polyquad was less toxic and less damaging to the ocular surface than BAK.

Alcon therefore considered the rose without thorns image, which must be viewed in its proper context by reference to the surrounding text and in light of the intended audience, complied with the Code, including Clauses 7.2, 7.3 and 7.10 (which Allergan cited without application to the facts):

- The image was not misleading as to the safety profile of the new Travatan formulation. The intended audience of ophthalmologists was well aware of the particular problems associated with the known ocular irritant, BAK, which was appropriately represented by thorns. The new formulation of Travatan no longer contained BAK and was therefore 'thorn' free. The image was therefore accurate, and not misleading.

- The image was not a misleading comparison between Alcon's product and a competitor's product; it unambiguously compared the original formulation of Travatan and the new BAK-free formulation – nothing more. The feature compared between the two formulations of Travatan (namely the presence/absence of BAK) was material, relevant and not misleading.

- The image was objective and did not exaggerate the properties of Travatan. The image was an appropriate metaphor for the absence of BAK in the new formulation, which was appropriately represented by thorns because BAK was a known ocular irritant, as supported by the literature and the special warning in the SPC. Therefore, the image did not imply that Travatan (BAK-free) had some special merit, quality or property which had not been substantiated.

Alcon therefore strongly disagreed with Allergan's interpretation of the rose without thorns image and considered its conclusions to be unfounded and alarmist.

PANEL RULING

The Panel noted that the complaint concerned the campaign visual of a thornless rose which presumably appeared on several promotional pieces. The Panel however, could not make an overarching ruling on material it had not seen and it thus considered the allegation solely in relation to the only piece provided by the complainant ie the advertisement at issue.

The Panel noted the picture of the thornless rose which ran down the left hand side of the advertisement. The prominent headline in the top right hand corner was 'Introducing BAK-free formulation Travatan'. In the Panel's view, most readers would associate the picture of the rose with the prominent headline and thus see the rose as representing Travatan without BAK.

The Panel considered that thorns on a rose stem would be seen as something injurious; the advertisement implied that Travatan preserved without BAK was free of such hazard. The Panel noted Alcon's submission about ophthalmic products containing BAK and the warning at Section 4.4 of their SPCs. The Panel noted that Section 4.4, Special warnings and precautions for use, of the SPC for Travatan preserved with BAK, included the statement '[BAK], which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since Travatan contains [BAK], close monitoring is required with frequent or prolonged use'. This statement was not in the BAK-free Travatan SPC although Section 4.8, Undesirable effects, of that SPC still listed punctate keratitis as a common (>1/100 to < 1/10) side effect of therapy. The Panel thus noted that Travatan preserved with Polyquad was still associated with one of the ocular side-effects referred to in Section 4.4 of the SPC for Travatan preserved with BAK. Further, Section 4.8 of the SPC for Travatan preserved with Polyquad listed another ten possible ocular adverse events which were also listed as possible adverse events in the SPC for Travatan preserved with BAK. In this regard the Panel did not consider that the thornless rose was a fair reflection of the side effect profile of Travatan preserved with Polyquad compared with Travatan preserved with BAK. The advertisement was misleading and exaggerated the difference between the two. A breach of Clauses 7.2, 7.3 and 7.10 was ruled.

The Panel did not consider that the thornless rose implied a potentially complete lack of side-effects as alleged; no breach of Clauses 7.2 and 7.10 was ruled.

The Panel did not consider that the visual in the advertisement implied any comparison with competitor products as alleged. No breach of Clause 7.3 was ruled.

APPEAL BY ALCON

Alcon appealed because, in its view, Allergan's complaint and the Panel's rulings of breaches of the Code were based, on a very limited view of the knowledge base relevant to the issues at hand, which were well known to, and appreciated by, those to whom the promotion of Travatan in general and the advertisement in particular was directed – ophthalomologists who specialised in the treatment of glaucoma. The complaint and rulings assumed a limited level of intelligence, knowledge and understanding that was incompatible with the target audience.

Alcon submitted that it reformulated Travatan because of the vast amount of experimental and clinical data available in the literature, and widely known to the ophthalmic community, about the potential ocular toxicity of long-term exposure to BAK, when used to preserve ophthalmic products. As a result of this data, labelling of all ophthalmic products preserved with BAK included a specific statutory warning to the effect that BAK might cause eye irritation. However, the realisation and understanding that the effects of BAK were more complex than this and more insidious had led to a greater interest in the use of alternative preservatives in ophthalmic products with the potential for long-term use, such as in glaucoma.

Alcon submitted that Baudouin (2008) was an excellent review about the detrimental effect of preservatives (particularly BAK) in eye drops and the implications for the treatment of glaucoma. The author made the following observations:

> 'In glaucoma, if effective, medical treatment is administered over the longterm, and therefore the majority of patients receive several decades of treatment. Based on data from clinical trials, the tolerability of glaucoma treatments seems satisfactory: few patients are withdrawn from medication as a result of local intolerance or allergy…..
>
> However, there are several major differences between clinical trials and the real-world progress of antiglaucoma therapy. Clinical trials are usually of short duration (6 months – 1 year). Patients with known hypersensitivity to the therapy or to the preservative contained within the product, and patients who have active ocular surface diseases such as dry eye, chronic allergy or severe blepharitis are often not included in such trials …. In population-based studies, the prevalence of dry eye in elderly patients (aged ≥ 65 years) varies between 15% and 34%... Impaired tear film may therefore interfere with topical treatments in a high proportion of patients, as the ocular surface disease may be encouraged by the drug(s) and/or preservatives, and may also reduce the resistance of the cornea and conjunctiva to the presence of toxic or irritant compounds.'

Allergan submitted that these observations were particularly relevant to this case, since they highlighted the fact that, although BAK was an acceptable ophthalmic preservative from a regulatory perspective, most ophthalmologists knew the limitations of regulatory studies and appreciated the more subtle effects that BAK might demonstrate in the long-term in a proportion of their patients. It was clear that problems with BAK were not universal and were a matter of degree, rather than being absolute. They could not therefore be considered simply with regard to the 'safety profile' of a product as indicated by the SPC or the results of regulatory studies designed to confirm currently acceptable levels of safety and efficacy but would only become apparent in appropriately designed, large, long-term studies, using appropriate assessment methods.

Numerous clinical studies had demonstrated the presence of ocular surface changes in glaucoma patients treated with BAK-containing medicines.

- A prospective epidemiological survey of 4107 glaucoma patients assessed the effects of preserved and preservative-free eye drops on ocular symptoms and conjunctival, corneal and palpebral signs in normal clinical practice (Pisella *et al* 2002). All symptoms of ocular surface disease (OSD) evaluated were significantly more prevalent in patients using preserved drops compared with those using preservative-free treatment. The prevalence of signs and symptoms was dose-dependent, increasing with the number of preserved eye drops used. In addition, when patients were either switched to preservative-free products or given fewer preservative-containing medicines, all symptoms and signs improved.

- Similar findings were obtained when pooled data from 9658 glaucoma patients were evaluated. The incidence of ocular signs and symptoms was significantly higher ($p<0.0001$) in patients receiving preserved eye drops, and it was observed that the incidence of these signs and symptoms could be decreased significantly ($p<0.0001$) by switching to a preservative-free formulation or by reducing the number of preservative-containing treatments (Jaenen *et al* 2007). Alcon noted that in this study and in Pisella *et al* (2002), the reference to preservative-containing treatments would almost certainly relate predominantly to products containing BAK since this was present in the vast majority of anti-glaucoma medications currently available. In the current edition of MIMS, of 25 other ocular hypotensive medicines listed, (excluding Travatan), 19 contained BAK, one contained benzododecinium bromide as the preservative and the other five were single dose, preservative-free preparations.

- A US study reported that 59% of patients with glaucoma or ocular hypertension had symptoms of OSD (Leung *et al* 2008). An association was demonstrated between the level of lissamine green staining of the conjunctiva, (an indicator of the presence of membrane damaged epithelial cells), and the number of BAK-preserved eye preparations, being used.

- A prospective observational study of 630 patients with primary open-angle glaucoma (POAG) or ocular hypertension, reported that 305 (48.4%) had mild, moderate or severe OSD symptoms (Fechtner *et al* 2010). OSD Index (OSDI) scores were significantly higher in those with a prior diagnosis of dry eye syndrome, but also varied with the number of IOP-lowering medications that were used. Again, most of these medicines would have been preserved with BAK.

- The basal tear turnover, (normal tear production, excluding reflex tearing), of 20 patients with open-angle glaucoma or ocular hypertension was measured by computerised objective fluorophotometry when using topical timolol preserved with BAK and two weeks after changing to topical preservative-free timolol (Kuppens *et al* 1995). The tear turnover of the patients before the change was 32% lower than that of healthy controls. A mean increase of 28% in the individual tear turnover values was noted after the change to the preservative-free timolol formulation ($p=0.04$).

- The effect of topical timolol with and without BAK on the epithelial permeability (a measure of cell membrane damage) and autofluorescence (a measure of cellular metabolism) of the cornea, was investigated in patients with POAG or ocular hypertension (de Jong *et al* 1994). The corneas of 21 patients were examined during treatment with timolol preserved with BAK at concentrations of 0.25% or 0.5%. After two weeks, patients were switched to treatment with timolol without BAK. Corneal epithelial permeability decreased significantly (mean decrease per patient 27%; $p=0.025$), whereas corneal autofluorescence increased significantly (mean increase per patient 6%; $p=0.003$) when switching to a BAK-free formulation. The authors considered that the results indicated that an improvement in corneal epithelial function occurred following the withdrawal of BAK.

- Numerous reports had also indicated that, even without evident symptoms or clinical manifestations, abnormal signs of inflammation were observed in the conjunctival epithelium of glaucoma patients. Immuno-inflammatory markers and mediators of the conjunctival epithelium of medically treated patients with glaucoma were found to be significantly increased, compared with healthy controls (Baudouin *et al* 2004; Baudouin, Pisella *et al* 2004). The intensity of this inflammatory reaction seemed to be related to the number of antiglaucoma medicines used, and the duration of treatment (Ariturk *et al* 1997).

Alcon submitted that it was clear from the above brief summary that the use of glaucoma medicines preserved with BAK had been associated with signs and symptoms of OSD, decrease in tear turnover rate, increased epithelial cell permeability and an increase in conjunctival inflammatory markers in the clinical situation. Alcon noted that the studies cited only represented a fraction of the information available in the literature relating to this situation. The effects of BAK on corneal and conjunctival epithelial cells in animal and *in vitro* models mirrored the clinical picture described above and had also provided further information concerning the underlying cellular mechanisms involved. As such, they were now used widely as predictive tools in research and data generated from these models was recognised and used by regulatory bodies worldwide.

- Pissela *et al* (2000) found that rabbits given a preserved beta-blocker (Timoptol 0.25% and 0.50%, preserved with 0.01% BAK) displayed a significantly greater reduction in tear film break-up time compared with those given a non-preserved beta-blocker containing the same concentrations of active, whilst Noecker *et al* (2004) found that treatment of rabbits with glaucoma medicines that contained higher levels of BAK resulted in greater damage to the cornea and conjunctiva compared with treatment with preparations preserved with lower concentrations of BAK.

- The effect of different concentrations of BAK (0.1–0.0001%) was studied on a continuous human conjunctival cell line: the Wong–Kilbourne derivative of Chang conjunctiva (De Saint Jean *et al* 1999). Cells were treated for 10 minutes and were assessed before treatment and at 3, 24, 48 and 72 hours after treatment. BAK at concentrations of 0.1% and 0.05% caused immediate cell lysis, while exposure to 0.01% BAK was associated with cell death within 24 hours. Doses of 0.005–0.0001% BAK induced apoptotic cell death at 24-72 hours in a dose-dependent manner.

- Pisella *et al* (2004) compared the toxicities of 0.005% latanoprost preserved with 0.02% BAK, 0.5% timolol preserved with 0.02% BAK, unpreserved 0.5% timolol and 0.02% BAK alone on the Wong–Kilbourne derived human conjunctival cell line. Cells were treated for 15 minutes and subsequently left to recover for 0, 4 and 24 hours in a normal medium. Both latanoprost and timolol were associated with toxic proapoptotic effects on conjunctival cells, whereas no toxic effect was observed with unpreserved timolol. Both medicines were less toxic than BAK alone.

- In another recent study, immortalized human conjunctival and corneal epithelial cells were exposed to BAK (0.001–0.1%) for one hour. It was found that BAK induced significant amounts of interleukin (IL-) 1 and tumour necrosis factor (TNF), but only moderate amounts of C-reactive protein (CRP), IL-10 and IL-12. Lower concentrations of BAK induced proportionally less elaboration (Epstein *et al* 2009).

Again, the above represented a mere sample of the confirmatory studies available in the literature.

In view of the extensive literature relating to the potential toxicity of BAK, and the high cost of treating glaucoma patients long-term with single use, preservative-free preparations, Alcon had developed two formulations of Travatan that were preserved with potentially less toxic preservatives.

Travatan Z, introduced into the US a number of years ago was preserved with sofZia, a proprietary oxidising preservative system. In clinical studies, Travatan Z produced a significant decrease in conjunctival hyperaemia and superficial punctate keratitis (SPK) severity in patients with open-angle glaucoma or ocular hypertension, who had previously been treated with latanoprost preserved with BAK (Aihara *et al* 2011; Yamazaki *et al* 2010). The level of SPK was a measure of corneal epithelial cell damage and the improvement noted was found to be maintained over one year of ongoing therapy (Aihara *et al*). Travatan Z had also been shown to produce a reduction in OSDI scores in problematic patients previously treated with latanoprost preserved with BAK, when used for up to 12 weeks (Katz *et al* 2010) and an improvement in mean OSDI scores in patients previously treated with latanoprost or bimatoprost (both preserved with BAK), who needed alternative therapy due to tolerability issues (Henry *et al* 2008). Finally, in another study, when 20 consecutive patients using latanoprost preserved with BAK were switched to Travatan Z, it was found that tear film break-up time, a measure of tear film instability, increased significantly when evaluated at eight weeks, while mean inferior corneal staining and mean OSDI scores both decreased significantly (Horsley and Kahook 2009).

Alcon submitted that, due to regulatory constraints, Travatan Z was not marketed in Europe but an alternative formulation, preserved with Polyquad, was developed for this market. Polyquad, a polyquarternary preservative, had a long history of safe and effective use in contact lens care and dry eye products in Europe and throughout the rest of the world. The ocular safety of Polyquad had also been compared with BAK in *in vitro* and animal models.

- *In vitro*, Polyquad-containing solutions had no discernible effects on the cytokinetic movement or on mitotic activity of human corneal epithelial cells, while BAK 0.01% caused immediate cell retraction and cessation of normal cytokinesis, cell movement and mitotic activity in the same model (Tripathi *et al* 1992).

- In a rabbit model, designed to evaluate the effect of artificial tear solutions on the corneal epithelial

barrier by measuring the uptake of carboxyfluorescein following exposure to test solutions, exposure to solutions containing 0.01% BAK caused an approximate 10 to 100-fold increase, while solutions preserved with Polyquad caused little or no increase (Lopez Bernal and Ubels 1991).

- More recently, Polyquad and BAK had been compared in an acute rat ocular toxicity model. Compared to Polyquad, BAK consistently and dramatically altered the corneo-conjunctival surface as evaluated by slit-lamp examination, fluorescein staining, impression cytology, in vivo confocal microscopy and histology. Although high concentrations of Polyquad had some effects on goblet cell density and some abnormalities were observed with in vivo confocal microscopy, when compared with an unpreserved balanced salt solution control, Polyquad was generally far less toxic than BAK in this model (Labbe *et al* 2006).

Alcon submitted that in the clinical situation, Polyquad had been used successfully for many years in artificial tears and ocular lubricants designed for long-term use. The potential effects of the preservative on the ocular surface were, however, difficult to evaluate in such products since they were used to ameliorate OSD. However, the low potential for ocular surface toxicity of Polyquad had been confirmed by its use in soft contact lens disinfecting and lubricating solutions. Soft contact lenses could act as a reservoir for preservative molecules on the eye and therefore could exacerbate any toxic effects that might be seen after normal ocular administration of eye drops. In numerous studies, solutions containing Polyquad induced minimal corneal staining in soft contact lens wearers and significantly lower levels of staining than solutions containing other cationic preservatives, such as polyhexanide (Jones *et al* 2002, Pritchard *et al* 2003, Jones *et al* 2005, Andrasko and Kelly 2008). The good ocular tolerance of Polyquad in soft contact lens wearers persisted in the longer-term (Gibbs *et al* 1989).

Alcon submitted that prior to launch of Travatan preserved with Polyquad, it was not feasible or practical to conduct long-term, large scale clinical studies designed to evaluate ocular safety and, given the substantial clinical database supporting the ocular safety of Polyquad, such studies were not necessary for regulatory purposes. However, the effects of Travatan preserved with Polyquad were evaluated in both rabbit and *in vitro* models.

- In the rabbit model, Travatan preserved with Polyquad was compared with phosphate-buffered saline, BAK 0.015% in water, Polyquad 0.001% in water, Travatan preserved with BAK (0.015%) and latanoprost preserved with BAK (0.02%). 50 µL of each solution was instilled 15 times, at 5 minute intervals, in both eyes of the rabbits. Assessments involved clinical observation of the rabbit eyes, *in vivo* confocal microscopy (IVCM), conjunctival impression cytology and immunohistological evaluation. Travatan preserved with Polyquad did not produce obvious irritation by clinical observation, changes in microstructures of the whole ocular surface as measured by *in vivo* confocal microscopy, inflammatory infiltration or cell damage as measured by impression cytology, altered levels of goblet cell counts or significant infiltration of CD45+ cells in the cornea. These findings were similar to those for phosphate-buffered saline and Polyquad 0.001% in water and significantly better than findings for Travatan preserved with BAK, latanoprost preserved with BAK and BAK 0.015% in water (Liang *et al* 2010).

- In an *in vitro* human conjunctival cell model, Travatan preserved with Polyquad was compared with phosphate-buffered saline, BAK 0.015% in water, BAK 0.02% in water, Polyquad 0.001% in water, Travatan preserved with BAK (0.015%) and latanoprost preserved with BAK (0.02%). Cells were incubated with the test compounds (50 µL/well) for 30 minutes at 37ºC with 98% humidity and 5% CO2. Six toxicological assays were used to assess three different cytotoxic responses: cell viability (neutral red, Alamar blue), apoptosis (YO-PRO-1, Hoechst 33342), and oxidative stress (H2DCF-DA, hydroethidine). In addition, the apoptosis and oxidative stress assays were each reported according to cell viability as observed with neutral red and Alamar blue. Travatan preserved with Polyquad demonstrated significantly improved cell viability and significantly less cytotoxicity, apoptosis and oxidative stress than any of the BAK-containing solutions (Brignole-Baudouin *et al* 2010).

- In a second *in vitro* investigation involving cultured human corneal and conjunctival epithelial cells, the effects of Travatan preserved with Polyquad on cell viability were compared with those of Travatan Z, sofZia vehicle, Travatan preserved with BAK, commercially available solutions containing latanoprost and tafluprost (both preserved with BAK) and a range of concentrations of BAK (0.001% to 0.05%). Cells were incubated with 100 µL of each solution for 25 minutes at 37ºC and 5% CO2. The toxicity of the prostaglandin analogues latanoprost, tafluprost and Travatan preserved with BAK was similar to the toxicity observed with their respective BAK concentrations. Travatan preserved with Polyquad and Travatan Z both provided significantly greater corneal and conjunctival cell survival than the BAK-preserved solutions. Travatan preserved with Polyquad demonstrated slightly improved survival of both corneal and conjunctival cells than Travatan Z, although the difference did not reach statistical significance in either case (Ammar *et al* 2010).

In summary Alcon submitted that in response to concerns about the potential effects on the ocular surface of long-term treatment of some patients

with glaucoma medicines preserved with BAK, it had developed two formulations of Travatan preserved with potentially less harmful preservatives, Polyquad and sofZia. The latter formulation was not available in Europe but had been on the US market for a number of years and had been the subject of a number of Phase IV post-marketing clinical studies, in contrast to Travatan preserved with Polyquad which had only recently obtained regulatory approval in Europe.

- The adverse effects of BAK-preserved medicines on the ocular surface had been demonstrated to be reversed, at least in a proportion of patients, when the medicines were replaced by preservative-free products, or, in the case of latanoprost and bimatoprost preserved with BAK, when substituted with Travatan Z, preserved with sofZia.

- The adverse effects of BAK-preserved glaucoma medicines observed in clinical studies had been duplicated in animal and *in vitro* models, which, therefore, provided powerful screening tools for use in the development of new formulations and a useful guide to glaucoma specialists of the likely clinical performance of these formulations. The usefulness and predictive value of such models was widely recognised by regulatory authorities and by ophthalmologists.

- Polyquad had an excellent ocular safety profile when used in soft contact lens care solutions and had been used for many years in artificial tears and ocular lubricants. In animal and *in vitro* models it had been clearly shown to be less toxic to corneal and conjunctival epithelial cells than BAK.

- In animal and *in vitro* models, Travatan preserved with Polyquad had a beneficial ocular safety profile compared with Travatan and latanoprost preserved with BAK and in an *in vitro* model it had at least a similar safety profile to Travatan Z.

With regard to the Panel's rulings, Alcon submitted that the thornless rose visual did not appear in isolation and must be interpreted in association with the accompanying text. The Panel noted that the prominent headline in the top right hand corner was 'Introducing BAK-free formulation Travatan'. In the Panel's view, most readers would associate the picture of the rose with the prominent headline and thus see the rose as representing Travatan without BAK. Alcon agreed with this association and indeed this was the intention of the advertisement. By extension, the thorns around the base of the stem must represent BAK. In its response above, Alcon made it clear that this was the interpretation intended by the association of the visual with the claim 'Introducing BAK-free formulation Travatan'.

Alcon noted that the Panel, however, 'considered that thorns on a rose stem would be seen as something injurious; the advertisement implied that Travatan preserved without BAK was free of such hazard'. Alcon disagreed with this interpretation, it was not the intention of the visual or the advertisement to convey such a message. Thorns on a rose were not generally associated with injury but regarded, at worse, as an inconvenience – something that was unfortunate and unwanted. This association resonated very well with the views of most ophthalmologists about the presence of BAK in glaucoma medicines. The attempt by Allergan and the Panel to associate the visual with the side effect profile of Travatan preserved with Polyquad was therefore flawed. This was particularly so because all glaucoma specialists knew that many of the local ocular side effects of current multidose prostaglandin analogue presentations eg irritation, hyperaemia, change in iris colouration, growth of eyelashes, change in skin pigmentation, were associated with the prostaglandin analogue molecule itself rather than BAK (Camras *et al* 1997). It was well known that the effects of BAK were more subtle and longer-term and were particularly associated with a sub-group of patients who either already had, or had a propensity to develop, OSD. Indeed, studies had indicated that the presence of prostaglandin analogues in a formulation could actually moderate, although not eliminate, some of the effects of BAK, which, in any event, were known to be dose dependent (Pisella *et al* 2004).

However, Alcon submitted that even in the unlikely event that a glaucoma specialist associated the thorns in the visual with the side effect profile of Travatan, the comparison attempted by the Panel would still be flawed.

The Panel noted that, 'Section 4.8, Undesirable effects, of that SPC [for Travatan preserved with Polyquad] still listed punctate keratitis as a common (>1/100 to <1/10) side effect of therapy. The Panel thus noted that Travatan preserved with Polyquad was still associated with one of the ocular side-effects referred to in Section 4.4 of the SPC for Travatan preserved with BAK. Further, Section 4.8 of the SPC for Travatan preserved with Polyquad listed another ten possible ocular adverse events which were also listed as possible adverse events in the SPC for Travatan preserved with BAK. In this regard the Panel did not consider that the thornless rose was a fair reflection of the side effect profile of Travatan preserved with Polyquad compared with Travatan preserved with BAK'.

Alcon submitted that it was widely recognised within the medical community that the comparative safety of two medicines could not be determined from information contained in their SPCs alone, particularly when one product had been marketed for a number of years and the other only recently introduced. Such comparisons could only be made as a result of appropriately designed and powered comparative clinical studies. The Panel knew that Travatan preserved with Polyquad was introduced as a result of a variation to Alcon's existing marketing authorization. Given that the change related to the replacement of one widely used

ophthalmic preservative with another, the regulatory focus for this variation was clinical efficacy and preservative efficacy. The long-term, large scale safety clinical studies required for registration of a new product were therefore not required in this case and the SPC for Travatan preserved with Polyquad, at this stage must clearly be expected to reflect this fact, and to build on the existing SPC, by any reasonable assessment. Alcon was therefore unclear why the Panel had tried to base its judgement solely on an SPC comparison in this case. It seemed highly unlikely that the visual in question, when viewed in the context of the advertisement, would seriously mislead a glaucoma specialist about the ocular safety profile of Travatan preserved with Polyquad as alleged. Alcon noted that the prescribing information for the product, which gave the appropriate details of the side effect profile, appeared at the bottom of the advertisement.

Alcon submitted that since it had established, and as agreed by the Panel, that the thorns in the visual represented BAK, the only comparison that could realistically be considered to be implied related not to the safety profile of the product but to the ocular safety profiles of BAK and Polyquad, when used in the concentrations necessary for appropriate preservative activity. This comparison was well established in the literature, as explained above, and was alluded to in the advertisement. The visual could, therefore, not be considered to mislead in this regard. However, Alcon noted that even this comparison was not the intention of the visual. As previously explained, the visual, in association with the words, 'Introducing BAK-free formulation Travatan', was simply intended to illustrate the complete removal of the 'unwanted' BAK from Travatan.

Alcon denied that breaches of Clauses 7.2, 7.3 and 7.10 since any comparison conveyed by the visual, in the context of the advertisement, was fair, accurate, capable of substantiation, not exaggerated and could not be considered to mislead the target audience, either directly or by implication.

COMMENTS FROM ALLERGAN

Allergan stated that this case did not relate to and nor did it take issue with the wealth of literature about the safety and efficacy profile of BAK. Indeed, Allergan understood the side effect profile of this preservative very well and was well aware of the precautions restricting use in certain patient groups, such as those with OSD. The crux of the complaint was about the lack of clinical evidence to support claims of an improved safety profile for Travatan preserved with Polyquad compared with Travatan preserved with BAK. Allergan did not consider that any such tolerability benefits had been demonstrated in clinical studies conducted by Alcon and therefore claims for an improved safety profile should not be made until proven in clinical studies.

Allergan considered that reference to Travatan Z (preserved with sofZia) introduced in the US and unavailable in the UK, was irrelevant.

Allergan did not consider the claims for Polyquad compared with BAK in *in vitro* and animal studies to be at issue here. However, Allergan strongly contested the application of these laboratory studies to demonstrate a clinical benefit in terms of tolerability for patients since it was not aware of any clinical studies to demonstrate this. Indeed, the only one clinical study which compared travoprost preserved with Polyquad and travoprost preserved with BAK showed that the safety profile was similar for both products (Denis *et al* 2010). The authors concluded that 'the safety profile of travoprost BAK free was similar to that of travoprost BAK'. The SPC for this new formulation also listed eye irritation, dry eye, pruritus, eye pain and ocular discomfort as common undesirable effects. Alcon had not supplied any additional clinical data comparing travoprost preserved with Polyquad and travoprost preserved with BAK to support its assertion of an improved safety profile within its advertisements.

Allergan alleged that it was disingenuous of Alcon to maintain that the rose visual was not intended to represent the tolerability profile of travoprost preserved with Polyquad. However, even if the line of argument was followed that the visual was intended to represent an absence of BAK, this in itself was misleading since the product was not preservative-free. Polyquad had not been used previously in treatments for glaucoma and as yet the tolerability profile of such treatments had not been established in large scale clinical studies.

Allergan considered Alcon's comments about the side effect profile listed in the SPC for travoprost preserved with Polyquad were fundamentally flawed. Promotion of a medicine must be in accordance with the terms of its marketing authorization and not be inconsistent with the particulars listed in its SPC. The side effects listed on the SPC for travoprost preserved with BAK must of course remain on the SPC until evidence from large scale clinical studies demonstrated an improved safety profile for travoprost preserved with Polyquad, which would permit their removal. However, Denis *et al* demonstrated a similar number of ocular adverse events for both travoprost preserved with Polyquad (n=185) and travoprost preserved with BAK (n=186); dry eye 5 (2.7%), 3 (1.6%), eye irritation 6 (3.2%), 9 (4.8%) and eye pruritus 7 (3.8%), 6 (3.2%) respectively.

Allergan agreed with Alcon that comparisons of the side effect profiles of two products could only be made via appropriately designed and powered clinical studies. Currently, there was no such evidence. Allergan alleged that Alcon's defence that because there was no further data from such studies for travoprost preserved with Polyquad, there were *de facto*, no such side effects, was fundamentally flawed and incorrect. Allergan agreed with the Panel's ruling on this matter and considered it appropriate that the Panel had ruled

on this matter based on the approved SPC for the product.

Allergan therefore agreed with the Panel's ruling that the thornless rose visual was not a fair reflection of the side effect profile of travatan preserved with Polyquad in breach of Clauses 7.2, 7.3 and 7.10.

APPEAL BOARD RULING

The Appeal Board considered that most people would view the thorns on a rose as injurious. The thornless rose in the context of the headline 'Introducing BAK-free formulation Travatan' implied that BAK-free Travatan was better tolerated than that preserved with BAK. However, the Appeal Board noted that the only direct clinical comparison of Travatan preserved with Polyquad and Travatan preserved with BAK (Denis *et al*) concluded that the safety profiles of the two were similar. The Appeal Board considered that the visual was misleading and exaggerated the difference between the two formulations of Travatan as alleged. The Appeal Board upheld the Panel's ruling of a breach of Clauses 7.2, 7.3 and 7.10. The appeal on this point was unsuccessful.

2 Advertisement – Implied claim for 'preservative free' and claim regarding side-effect profile

COMPLAINT

Allergan alleged that the claim 'Travatan BAK-free', used to alert customers to the newly formulated Travatan, misled as it implied that the product was preservative-free, when in fact it was preserved with Polyquad. This preservative was clearly not 'side-effect free' as was generally implied in the advertisement and with the campaign visual. Allergan also considered the use of laboratory studies within the advertisement was unacceptable to support general claims regarding tolerability. Allergan was not aware of any clinical data to support the tolerability claims made in the advertisement for Polyquad when compared with BAK.

Allergan noted that Denis *et al* demonstrated a similar number of ocular adverse events for both Travatan preserved with Polyquad and Travatan preserved with BAK; dry eye 5 (2.7%) and 3 (1.6%), eye irritation 6 (3.2%) and 9 (4.8%) and eye pruritus 7 (3.8%) and 6 (3.2%) respectively.

The claims were therefore misleading in breach of Clauses 7.2, 7.3 and 7.10. In inter-company dialogue, Alcon considered the information that it presented regarding laboratory studies to be permissible and that extrapolation of findings relating to the relative behaviour of Travatan in these models was of direct relevance and clinical significance. Allergan disagreed since it was generally established that laboratory studies which showed significant differences between products did not necessarily translate into clinical differences in patients. In this instance, this was indeed the case as Denis *et al* demonstrated a similar level of ocular adverse events for Travatan preserved with Polyquad and Travatan preserved with BAK.

Allergan was concerned that clinicians would take away from this campaign that Travatan (preserved with Polyquad) was a preservative-free product and that it had an improved safety profile vs the previous formulation preserved with BAK; both messages were incorrect and misleading. Allergan believed this had been a deliberate campaign to mislead clinicians as to the safety profile of Travatan preserved with Polyquad. Due to the serious nature of its concerns, and the fact that the misleading visual related to the safety profile for Travatan and might prejudice patient safety, Allergan also alleged that the campaign visual breached Clause 9.1.

RESPONSE

Alcon found Allergan's suggestion that BAK-free implied that the Travatan was preservative-free difficult to understand. There was an asterisk immediately after the first use of the term that drew attention to a footnote that made it clear that BAK related to benzalkonium chloride. Further, the statement in the advertisement immediately following the heading in large, clear, bold text was: 'A multidose prostaglandin analogue with POLYQUAD'. Alcon noted that Polyquad was an already established preservative which had been used in ophthalmic preparations, such as contact lens solutions for around 20 years and so was well known by ophthalmologists. Therefore, the claim did not imply that the product was preservative-free, only that it did not contain BAK as the preservative. This was an important and relevant claim to make as there were well documented advantages to removing BAK from ocular medicines. The benefits of Travatan BAK-free had been demonstrated in laboratory studies which showed the benefits of using Polyquad over BAK and these benefits were further substantiated by the removal from the SPC of the special warning in Section 4.4. Alcon therefore could not accept that BAK-free, as it appeared in the advertisement, could possibly be misinterpreted by the expert audience to whom it was addressed, and the statement was not misleading.

The assertion from Allergan that the rose without thorns suggested Travatan was 'side-effect free' was nonsensical. Rather, Alcon had stated that Polyquad had been shown to be 'gentler' and 'less toxic', not that the new Travatan formulation did not have any side-effects. These claims had been made in text which was clear, placed in an obvious position and in an appropriately large font. Therefore, it was hard to believe that the intended audience within the ophthalmic field (who were already highly knowledgeable about glaucoma medicines) could be misled in this way, particularly in light of the surrounding text, but also considering that both the prescribing information and SPC for the product

were readily available to them. As explained above, Alcon had not implied that overall Travatan had an improved ocular safety profile, either by reference to Denis *et al* (a non-inferiority study), or in any other way.

Alcon believed that the extrapolation of laboratory data to the clinical situation was permissible in this instance. It was made clear in the advertisement that the data was derived from 'laboratory studies' (second bullet point) and '*in vitro*' studies (third bullet point). The non-clinical data that was referenced with regard to the BAK-free formulation of Travatan was based on well established *in vivo* animal models and *in vitro* models which used cultured human conjunctival epithelial cells that were sufficiently robust to be included in the variation to the marketing authorization for the reformulation of Travatan, assessed by the European Medicines Agency (EMA). Indeed, the use of laboratory data derived from well established models was commonplace in this field. Allergan would be well aware of this considering that, to support the registration of its product Lumigan, it had conducted six pharmacokinetic laboratory studies in rabbits (both *in vitro* and *in vivo*). These studies were accepted by the Committee for Medicinal Products for Human Use (CHMP) and were cited in the European Public Assessment Report (EPAR) for Lumigan (EMA/105752/2010). In the circumstances described above, and considering that laboratory data derived from well established models had been consistently acceptable for the CHMP/EMA in this field, it was appropriate to extrapolate the findings of the studies cited in the advertisement (based on well established models) to support the general claims in the promotional campaign. Alcon further noted in the Lumigan EPAR that, due to the cytotoxic properties of BAK 'it is, from a safety point of view, preferable to minimise its presence in ophthalmic preparations' and, in this context, Allergan submitted preliminary results from a newly conducted ocular absorption study in rabbits in response to the CHMP's request to substantiate why similar efficacy could not be obtained with a formulation containing a lower BAK concentration.

Alcon referred to Allergan's asserted that clinicians would take away from the campaign two incorrect and misleading messages ie that Travatan was preservative-free and had an improved safety profile vs the previous formulation preserved with BAK. Alcon maintained that the advertisement was compliant with the Code, including Clauses 7.2, 7.3, 7.10 and 9.1, as explained below.

- Alcon had not implied that the new formulation was preservative-free; rather, it had specifically stated that the new formulation was 'with POLYQUAD', a well-known preservative. Further, that the new formulation was 'BAK-free' was an accurate and relevant statement which was important to highlight to ophthalmologists. Stating that Travatan was BAK-free, and illustrating this with the rose without thorns image did not imply that the new formulation was side-effect free.

- In relation to the campaign visual, the advertisement could not be considered to be a misleading comparison between Alcon's product and a competitor's product; the image unambiguously compared the original formulation of Travatan and the new BAK-free formulation – nothing more. The feature compared between the two formulations of Travatan (namely the presence/absence of BAK) was material, relevant and not misleading.

- The presentation of the new Travatan formulation was objective, tempered and did not compromise rational use of the medicine. The rose without thorns image was unambiguous in light of the accompanying text which explained that laboratory and *in vitro* studies had demonstrated that Polyquad was 'gentler' and 'less toxic' compared with BAK. The advertisement did not imply that Travatan (BAK-free) had some special merit, quality or property which had not been substantiated; the advantages of removing BAK were well-known.

Finally, Alcon strongly refuted that it had engaged in a deliberate campaign to mislead clinicians as to the safety profile of the new formulation of Travatan. This allegation was unfair and unsubstantiated. Those within the ophthalmic field would not be misled into believing that the removal of BAK equated to an absence of all side-effects or an improved safety profile overall. Further, ophthalmologists would understand why the known ocular irritant, BAK, was likened to thorns. Alcon could not accept that the advertisement (or indeed the campaign more generally) might prejudice patient safety; this statement was alarmist and unjustified. In these circumstances, Alcon believed that it had not compromised high standards in breach of Clause 9.1.

PANEL RULING

The Panel did not consider that the claims that Travatan was BAK-free implied that it was also preservative-free. The advertisement clearly referred to 'A multidose prostaglandin analogue with POLYQUAD'. In the Panel's view, readers of the British Journal of Ophthalmology would be familiar with Polyquad as a preservative and never expect a multidose presentation to be preservative-free. The Panel did not consider that the claims were misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that the advertisement included, *inter alia*, the claim 'Contains Polyquad, which had demonstrated a gentler effect on the ocular surface than BAK in laboratory studies'. The studies cited in support of this claim (Labbé *et al* 2006 and Liang *et al* 2010) compared the ocular surface toxicity of BAK and Polyquad in rats and rabbits respectively. Both studies reported that Polyquad was less toxic than

BAK but both groups noted that ophthalmic medicines were intended for long-term treatment and as the studies had taken place over a short time period, the long-term safety of Polyquad had not been examined. Nonetheless, Polyquad might be a suitable replacement for BAK.

The advertisement also included the claim 'Significantly less toxic to human conjunctive and coneal epithlial cells when compared to latanoprost solutions (preserved with 0.02% BAK *in vitro*)'. This claim was referenced to Brignole-Baudouin *et al* (2010) which assessed the cytotoxicity on isolated human conjunctival epithelial cells of Travatan preserved with Polyquad vs Travatan preserved with BAK. The authors concluded that their results supported the safety of BAK-free Travatan and that, by implication formulations preserved with Polyquad might be better for ocular surface health than solutions containing BAK.

The Panel noted that the supplementary information to Clause 7.2 stated that care must be taken with, *inter alia*, *in vitro* or animal studies so as not to mislead with regard to their significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. In contrast to the animal and *in vitro* studies cited above, Denis *et al* was a 3 month double-blind, randomized, parallel group, non-inferiority clinical study to compare the efficacy of Travatan preserved with BAK vs Travatan preserved with Polyquad. The authors reported that no clinically relevant differences in the adverse event profile of the two formulations were identified.

The Panel considered that the animal and *in vitro* studies cited in the advertisement implied that BAK-free Travatan had a better safety profile compared with Travatan preserved with BAK. The only direct clinical comparison of the two (Denis *et al*) did not show that to be the case. The Panel considered that the advertisement was misleading and exaggerated in that regard. A breach of Clauses 7.2, 7.3 and 7.10 was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

APPEAL BY ALCON

Alcon submitted that the claims in the advertisement citing animal and *in vitro* studies were factual, clear and unambiguous and every attempt was made to ensure that they could not be misinterpreted and that they did not mislead, either directly or by implication.

The claims noted by the Panel were, 'Contains Polyquad, which has demonstrated a gentler effect on the ocular surface than BAK in laboratory studies,' and, 'Significantly less toxic to human conjunctival and corneal epithlial cells when compared to latanoprost solution (preserved with 0.02% BAK *in vitro*)'. Alcon submitted that both claims were suitably referenced statements of fact, which did not mislead or misrepresent. However, the Panel, 'noted that the supplementary information to Clause 7.2 stated that care must be taken with, *inter alia*, *in vitro* or animal studies so as not to mislead with regard to their significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance'. In contrast to the animal and *in vitro* studies cited above, Denis *et al* was a three month, double-blind, randomized, parallel group, non-inferiority clinical study to compare the efficacy of Travatan preserved with BAK with that of Travatan preserved with Polyquad. The authors reported that 'no clinically relevant differences in the adverse event profile of the two formulations were identified'.

Alcon submitted that it had taken the supplementary information to Clause 7.2 into account when preparing the advertisement. With regard to the Panel's rulings, Alcon observed that:

- The claims at issue did not directly extrapolate the animal and *in vitro* data presented to the clinical situation. This extrapolation had been implied by the Panel although this was not unreasonable given the very strong association established in the literature between the results of animal and *in vitro* data, of the type presented, and the clinical situation with regard to treatment of glaucoma.

- Denis *et al* was a regulatory study designed to demonstrate non-inferiority in terms of IOP-reducing efficacy of Travatan preserved with Polyquad, when compared with Travatan preserved with BAK. It was of only three months' duration and included a number and profile of subjects appropriate for its intended objective. The study also did not include the specialised testing needed to detect differences relating to the known long-term effects of BAK, such as measurement of tear film break-up time, OSDI type questionnaires, impression cytology etc. The study was therefore not intended to or designed to detect long-term differences in the effects of the two formulations on ocular surface health. Such studies could take many years to complete and were almost certain to be Type IV post-marketing studies. It was therefore unreasonable to expect such studies to have been conducted at the time of product launch. As such, the Panel's conclusions, based solely on Denis *et al*, were invalid.

- A very strong correlation had been established in the literature between the type of animal and *in vitro* data cited in the advertisement for Polyquad and Travatan preserved with Polyquad and the observations relating to the treatment of glaucoma as made clear by the summary of data presented above. In Alcon's view, therefore, there was a clear rationale to confirm that the animal and *in vitro* data cited was of direct relevance

and significance to the clinical situation. The advertisement, however, did not overstate or exaggerate this relevance and significance and therefore did not mislead.

Alcon noted that Clause 7.2 stated that, 'Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine'. Given the strong association between animal and *in vitro* data relating to the effects of glaucoma medicines on the ocular surface and the effects observed in clinical practice, withholding information about the known ocular safety profile of Polyquad and Travatan preserved with Polyquad, obtained from animal and *in vitro* studies, simply because confirmatory long-term clinical studies had not been conducted, would have contravened Clause 7.2. It was therefore puzzling that in its rulings, the Panel appeared to endorse such a course of action.

Alcon denied breaches of Clauses 7.2, 7.3 and 7.10 since the reference to animal and *in vitro* data did not attempt to mislead with regard to their relevance or significance, nor did it directly attempt to extrapolate the data to the clinical situation. In any event, there was data to show that the animal and *in vitro* data cited was of direct relevance and significance to the clinical situation and withholding the information, which would help a clinician to form an opinion of the therapeutic value of the medicine, could be considered to be a breach of Clause 7.2. By providing this information, but making the source very clear, Alcon enabled the clinician to judge its relevance based on his own expert opinion and experience.

Alcon noted that Allergan stated that, due to the serious nature of its concerns, and the fact that this misleading visual related to the safely profile for Travatan and might prejudice patient safety, the campaign visual breached Clause 9.1. The alleged breach of Clause 9.1 thus related to the visual only, and not to the advertisement as a whole, and also implied that its use could prejudice patient safety. Since there was no convincing data to clearly prove either an efficacy or safety disadvantage for patients using Travatan preserved with Polyquad, compared to other medical treatments for glaucoma, Alcon concluded that Allergan's allegation was exaggerated and unsubstantiated. Since the Panel did not refer to this part of Allergan's complaint, Alcon assumed that it did not agree with it.

Alcon submitted that the ruling of a breach of Clause 9.1 therefore rested solely on the previous rulings of breaches in Clauses 7.2, 7.3 and 7.10. Since Alcon had demonstrated above that no breaches of those clauses had taken place, it followed that there had also been no breach of Clause 9.1. Given the nature of the regulatory process required and the data that needed to be generated to introduce the reformulated version of Travatan, combined with the need to comply fully with the requirements of Clause 7.2 of the Code, it was clear that the highest standards had been maintained at all times. Even in the event of a ruling of any breach of Clauses 7.2, 7.3 and 7.10, Alcon submitted that this would be a technicality resulting from an unintentional misunderstanding and that a finding of a breach of Clause 9.1 was therefore inappropriate.

COMMENTS FROM ALLERGAN

Allergan alleged that the animal and *in vitro* studies cited in the advertisement implied that BAK-free Travatan had a better safety profile compared with Travatan preserved with BAK, while the only direct clinical comparison of the two (Denis *et al*) did not show that to be the case. The advertisement was therefore misleading and exaggerated in that regard in breach of Clauses 7.2, 7.3 and 7.10.

Allergan alleged that the presentation of the claims for Polyquad compared with BAK in *in vitro* and animal studies to be the fundamental issue of this complaint. Allergan was concerned about the use of these studies to support claims for an improved safety profile for travoprost preserved with Polyquad. This was particularly pertinent when considering Denis *et al*. Whilst Allergan accepted that this study was for registration purposes only and designed to show non-inferiority in terms of efficacy, it was still the only clinical study to compare travoprost preserved with Polyquad and travoprost preserved with BAK. Allergan also understood that this study was not designed to detect any differences relating to the specific effects of Polyquad or BAK. However, this was the only clinical data available and it did not support the claims made for an improved ocular safety profile for travoprost preserved with Polyquad compared with travoprost preserved with BAK.

Allergan agreed that material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. However, Allergan disputed that Alcon had provided sufficient information to enable the recipient to do this by incorrectly presenting data from laboratory studies to support clinical claims for ocular tolerability. Alcon maintained that the information that it presented regarding laboratory studies was permissible and that there was a rationale for information from these models to be presented because it was of direct relevance and clinical significance. Allergan did not consider this to be the case since it was generally established that laboratory studies showing differences between products did not necessarily translate into clinical differences in patients.

Allergan therefore agreed with the Panel's ruling that the presentation of animal and *in vitro* data in this advertisement was misleading and exaggerated in breach of Clauses 7.2, 7.3 and 7.10.

Allergan alleged that this advertisement was misleading as it implied a safety benefit for the product that could not be substantiated and thus might prejudice patient safety. Alcon stated in its

response that since there was no convincing data to clearly prove either an efficacy or safety disadvantage for patients using Travatan preserved with Polyquad compared with other treatments, Allergan's concerns were exaggerated and unsubstantiated. However, Allergan took the opposing view that there was no convincing data to prove either an efficacy or safety advantage for patients using travoprost preserved with Polyquad compared with other treatments and therefore no such safety benefit claims could be supported.

Allergan agreed with the Panel's ruling that high standards had therefore not been maintained and hence there had been a breach of Clause 9.1.

In summary, Allergan was concerned that recipients of this material would be misled as to the significance of the ocular safety data implied by the thornless rose visual. The core issue of Allergan's concerns was that there was an implied clinical benefit for travoprost preserved with Polyquad with no supporting clinical data.

APPEAL BOARD RULING

The Appeal Board noted that under the heading 'Travatan BAK-free formulation:' the advertisement featured two bullet points which referred to animal and *in vitro* studies. In particular the claim 'Significantly less toxic to human conjunctive and corneal epithelial cells when compared to latanoprost solutions (preserved with 0.02% BAK *in vitro*)' was referenced to Brignole-Baudouin *et al* which compared the effects of Travatan BAK-free with travoprost and lantaprost which were both preserved with BAK on isolated human conjunctival epithelial cells. The Appeal Board noted that the authors stated that '…formulations preserved with Polyquad *might* be better for ocular surface health than solutions containing BAK' (emphasis added). In the Appeal Board's view 'Significantly less toxic…' as used in the advertisement was quite different to '…might be better…', as used by Brignole-Baudouin *et al*. The Appeal Board considered that in that regard the claim did not reflect the cited paper.

The Appeal Board considered that although the results of *in vitro* models might predict future clinical effects there was no guarantee that this would be so. When presenting animal and *in vitro* studies care was needed to ensure that, in the absence of clinical evidence, clinical effects were not inferred or claimed. The Appeal Board noted, as in point 1, that the only clinical evidence available (Denis *et al*) concluded that the safety profile of Travatan preserved with Polyquad was similar to that preserved with BAK.

The Appeal Board considered that the *in vitro* and animal data presented in the advertisement implied that BAK-free Travatan was better tolerated than that preserved with BAK and this was not supported by the available clinical data. The Appeal Board considered that the advertisement was misleading and exaggerated in that regard. The Appeal Board upheld the Panel's ruling of a breach of Clauses 7.2, 7.3 and 7.10. The appeal on this point was unsuccessful.

The Appeal Board noted its rulings above and considered that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

Complaint received **21 February 2011**

Case completed **9 June 2011**

ANONYMOUS REPRESENTATIVE v ALCON

Promotion of Azarga

An anonymous Alcon representative complained about the company's alleged unethical promotion of Azarga (brinzolamide/timolol) eye drops for glaucoma. The complainant explained that representatives had been given litmus paper and bottles of Azarga and Cosopt (a competitor product) in order to practically demonstrate the pH differences between the two. The complainant alleged that representatives had been encouraged to instil the eye drops into their own eyes and those of their customers; one doctor had reportedly suffered an adverse event. The complainant stated that representatives were asked by their managers to 'dampen down' on the practice as the competition was upset but submitted that the sensationalism had worked too well for any of his team to stop.

The detailed response from Alcon is given below.

The Panel noted that a complainant had the burden of proving their complaint on the balance of probabilities. Anonymous complaints, like all complaints were judged on the evidence provided by both parties. In this case, the complainant had provided no evidence to support their allegations and as they had also not provided any contact details there was no way to ask them to provide further and better particulars.

The Panel noted that one page of the Azarga detail aid highlighted the difference in pH between Azarga and Cosopt. One of the slides from the representatives' briefing showed bottles of both eye drops and some litmus paper. In the Panel's view it was not unreasonable for representatives to practically demonstrate the pH difference between the two products. It was not unacceptable under the Code for representatives to hold supplies of medicines and Alcon's record of the quantity and destination of all of the eye drops supplied to the field force did not seem incompatible with their use to demonstrate pH differences.

The Panel noted that representatives had been asked to demonstrate the pH differences between Azarga and Cosopt in February 2010, a year before the complaint was received; despite the passage of time the complainant had provided no evidence to show that representatives had been encouraged to instil the eye drops either into their own eyes or those of their customers. Neither had any evidence been provided to show that managers had instructed the representatives to 'dampen down' the practice. The Panel noted Alcon's submission that it was not unusual for an ophthalmologist to unilaterally decide to try eye drops out on themselves so that they knew if, and how much, discomfort each produced on instillation. In the Panel's view it was not unreasonable that the ophthalmologists might report the results back to the representatives.

The Panel noted that the representatives had not been trained on how to instil eye drops. It would have been helpful, given ophthalmologists' propensity to try out eye drops, to have reminded representatives not to let them use the demonstration bottles. However, there was no evidence that representatives had been briefed to instil the eye drops either into their own eyes or those of their customers as alleged and no evidence that representatives had proactively encouraged ophthalmologists to instil the demonstration eye drops. No breach of the Code was ruled.

The eye drops had not been provided as samples and so there could thus be no breach of the Code in that regard.

The Panel noted its rulings above and considered that there was no evidence to show that high standards had not been maintained. No breach of the Code was ruled including no breach of Clause 2.

An anonymous, non-contactable representative of Alcon Laboratories (UK) Limited, complained about the company's alleged unethical promotion of Azarga (brinzolamide/timolol), an eye drop preparation for the treatment of glaucoma.

COMPLAINT

The complainant submitted that in late 2010 representatives were given litmus paper and samples of Azarga and a competitor product, Cosopt, to use in sales calls to highlight 'huge' pH differences between the two products. A number of colleagues had been very concerned that representatives had the medicines at all but even more alarming was that many had been 'encouraged' to instil the eye drops either into their own eyes or into the eyes of their customers. The complainant stated that he had been horrified to hear that lots of doctors actually tried a drop in each eye first of all but the fact that the representatives were not health professionals but had administered prescription only medicines and that one doctor had an adverse event as he was beta blocker intolerant (the incident was not reported as the doctor was a friend of the representative), was frankly disgusting!

The complainant stated that representatives were asked by their managers to dampen down on the practice just before Christmas as the competition was upset but submitted that the sensationalism had worked too well for any of his team to stop!

In the complainant's view, the competition in this case was too weak to complain as Alcon had beaten it on a number of occasions already but the complainant was very worried about a complaint about him personally so wanted to bring some of the unethical behaviour he was being pushed to do to the Authority's attention.

When writing to Alcon, the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2, 15.9 and 17 of the 2008 Code.

RESPONSE

Alcon stated that the complaint appeared to relate to a product demonstration that was introduced to its medical sales representatives in February 2010. This demonstration was intended to assist in the promotion of Azarga, which was a fixed-dose combination, topical anti-glaucoma therapy containing the beta-blocker, timolol, and the carbonic anhydrase inhibitor, brinzolamide. There was only one other similar combination product on the market, Cosopt, marketed by Merck Sharp & Dohme, which also contained timolol but in combination with dorzolamide. Both products were designed to reduce raised intraocular pressure in patients suffering from glaucoma or ocular hypertension. Since Cosopt was the first product of this type to be introduced in the UK, it currently had a greater market share. It was therefore understandable that the main focus of Alcon's promotional efforts for Azarga was a comparison of the product with Cosopt.

Clinical studies had demonstrated no statistically significant difference in efficacy between Azarga and Cosopt. However, Cosopt produced statistically significantly more stinging and discomfort upon instillation than Azarga. This difference was attributed to a difference in the pH of the two products. Tears had a pH that was close to neutral (pH 7) and it was generally considered that, for maximum comfort upon instillation, an eye drop should also have a pH that was as close to neutral as possible. Azarga had a pH of 7.2, while Cosopt had the much more acidic pH of 5.6. This difference between the products had been emphasised in Alcon's promotional material, where it had been illustrated by the colour difference obtained when the two products were applied to a pH indicator strip. It was suggested during a sales cycle meeting that this message could be reinforced during a sales representative's detail by a practical demonstration in which a drop of each product was applied to pH indicator paper in front of the doctor. The colours produced could then be related to the visual in Alcon's promotional material to support the claim made.

For this reason, all representatives (approximately 30) were give 1 or 2 bottles of Azarga and Cosopt (consistent with the purpose intended), and strips of pH indicator paper. The quantity, details and destination of all product supplied for this purpose were recorded and after this initial, very limited supply, further supplies of product had to be requested by a representative in writing and these supplies were also recorded, so that it could be confirmed, based on the call pattern of the representative, that product was only being used as intended. Alcon's records showed that 77 bottles of Cosopt had been provided to representatives since the initiative was started, the last of which was provided in December 2010.

Alcon noted that the eye drops supplied should not be considered as 'samples' as defined in Clause 17, since they were not intended to be handed over or delivered to a health professional and were for the use of the representative only in the manner described. The strict control and documentation of the quantity supplied ensured that eye drops were only being used as intended and it was clear from Alcon's records that no product could have been left with health professionals as 'samples'.

The briefing material used for this programme was page 6 of the Azarga detail aid used in February 2010. A copy of detail aid was provided for information (it was superseded in May 2010). In addition, a slide conveying the essence of the demonstration, containing images of the two eye drops and the pH indicator paper to be used, was displayed during the briefing at a sales cycle meeting held in January 2010 and a copy of this presentation was provided. The slide contained a build so that the product images were displayed initially, followed by the pH values and finally the image of the pH indicator paper. No further briefing material was considered to be necessary, since the demonstration was such a simple procedure and a practical demonstration was also given at the time.

The product demonstration programme that was instituted to support the promotion of Azarga, that Alcon believed formed the basis of this complaint, was outlined above. Alcon could not comment further on the allegations since they appeared to be unsubstantiated and disingenuous and were not consistent with the briefing given to Alcon's representatives. In Alcon's view, if the complainant's grievances were genuine, then the representative or representatives in question would have at least broached the matter with line management or with Alcon's human resources department (which would deal confidentially with such matters). No such representation had been made. In any event, the idea that an ophthalmologist would allow a representative to instil an eye drop into their eyes, which seemed to be the implication in the complaint, was beyond comprehension. It might be that a misunderstanding arose on the part of the complainant because some ophthalmologists decided unilaterally to try the two products in their own eyes; indeed Alcon was aware that this happened on a handful of occasions. However, this was not the objective of the demonstration and Alcon could not be responsible for actions taken by the ophthalmologists on their own initiative. Alcon was not aware that any of its representatives tried the drops in their own eyes as suggested, and in any event no evidence had been provided for this

allegation. In addition, the assertion that Alcon's competitor was 'too weak' to protect its own interests was also not consistent with Alcon's experience, nor, it believed, with that of the PMCPA and, in Alcon's opinion, raised further doubt about the validity of the complaint. Alcon had, however, instructed representatives to cease this activity pending the Panel's ruling.

In response to a request for further information, Alcon submitted that, as described above, its representatives had been instructed to demonstrate the pH difference between Azarga and Cosopt. This demonstration formed part of Alcon's promotional strategy, which concentrated on highlighting comfort differences between Azarga and the current market leader, an attribute which Alcon considered would have a positive influence on patient compliance. Alcon noted that it had stated that it knew, through its representatives, that some ophthalmologists had decided unilaterally to try Azarga and Cosopt in their own eyes. Alcon stated that it could not provide more details and noted that it was not unusual for an ophthalmologist to instil an eye drop into their own eye(s), to enable them to appreciate drop comfort. Compliance with therapy was extremely important for glaucoma patients and could be influenced by any significant discomfort produced when an eye drop was instilled. Glaucoma specialists therefore occasionally liked to make a personal comparison of the type described to assist in differentiating between treatments that appeared to have similar efficacy.

In view of the above, Alcon would not necessarily record every occasion upon which an ophthalmologist told the company that they had tried one of its products or a competitor product personally and so could not confirm accurately how common this practice was, or provide details on the source of product used on each occasion. Alcon, however, confirmed that it had no record that any of its representatives had instilled any eye drop into customers' eyes as alleged. The company also confirmed that its representatives were not given any practical training concerning instillation of eye drops, since it was not considered that that was relevant to the performance of their duties.

In addition, Alcon did not consider that there was any reason why an ophthalmologist should not try products in this way, if they chose to do so, and did not believe that it was the company's responsibility to pass any comment on the practice.

PANEL RULING

The Panel noted that the Constitution and Procedure clearly stated that a complainant had the burden of proving their complaint on the balance of probabilities. Anonymous complaints, like all complaints were judged on the evidence provided by both parties. The Panel noted that in this case, the complainant had provided no evidence to support their allegations and as they had also not provided any contact details there was no way to ask them to provide further and better particulars.

The Panel noted that one page of the Azarga detail aid highlighted the difference in pH between Azarga and Cosopt. One of the slides from the representatives' briefing showed bottles of both eye drops and some litmus paper. In the Panel's view it was not unreasonable for representatives to practically demonstrate the pH difference between the two products. It was not unacceptable under the Code for representatives to hold supplies of medicines and the Panel noted Alcon's submission that it had recorded the quantity, details and destination of all of the eye drops supplied to the field force. The product demonstration was introduced to the 30 or so representatives in February 2010 and by December of that year 77 bottles of Cosopt had been supplied. In the Panel's view this quantity did not seem incompatible with their use to demonstrate pH differences.

The Panel noted that representatives had been asked to demonstrate the pH differences between Azarga and Cosopt in February 2010, a year before the complaint was received; despite the passage of time the complainant had provided no evidence to show that representatives had been encouraged to instil the eye drops either into their own eyes or those of their customers. Neither had any evidence been provided to show that managers had instructed the representatives to 'dampen down' the practice. The Panel noted Alcon's submission that it was not unusual for an ophthalmologist to unilaterally decide to try eye drops out on themselves so that they knew if, and how much, discomfort each produced on instillation. In the Panel's view it was not unreasonable that the ophthalmologists might report the results back to the representatives.

The Panel noted that the representatives had not been trained on how to instil eye drops. It would have been helpful, given ophthalmologists' propensity to try out eye drops, to have reminded representatives not to let them use the demonstration bottles. However, there was no evidence that representatives had been briefed to instil the eye drops either into their own eyes or those of their customers as alleged; no breach of Clause 15.9 was ruled. There was no evidence that representatives had proactively encouraged ophthalmologists to instil the demonstration eye drops. No breach of Clause 15.2 was ruled.

The Panel noted that the eye drops provided to the representatives had not been provided as samples to be given to a health professional so that they might familiarize themselves with them and acquire experience in dealing with them. There could thus be no breach of Clause 17.

The Panel noted its rulings above and considered that there was no evidence to show that high standards had not been maintained. No breach of Clause 9.1 was ruled. It thus followed that there could be no breach of Clause 2.

Complaint received **21 February 2011**

Case completed **27 April 2011**

TAKEDA v ASTRAZENECA

Zoladex letter

Takeda complained about a Zoladex (goserelin) letter. The letter informed readers of Zoladex price reduction and also compared the efficacy of Zoladex with, *inter alia*, Takeda's product. Prostap (leuprorelin).

Zoladex and Prostap were both luteinising hormone releasing hormone analogues (LHRHa) indicated for the treatment of prostate cancer.

Takeda alleged that the claim: *'No other LHRHa* has demonstrated survival benefit in all 3 stages of prostate cancer' was an absolute claim based on strict inclusion and exclusion criteria (ie randomized controlled trials of the UK dose comparing LHRHa monotherapy with a standard comparator, combined androgen blockade omitted) and the initial impression was altered by reading the subsequent footnote. Takeda alleged that the claim was an exaggerated and unbalanced view of the evidence and thus misleading; survival benefit in all three stages of prostate cancer with Prostap had been demonstrated and Takeda cited a number of studies in support of its position. Takeda further alleged that the claim was in bold and thus unduly emphasized.

The rationale for omitting combined androgen blockade data was unclear and did not reflect clinical practice and the totality of Prostap evidence. A long-term study comparing leuprorelin monotherapy vs continuous combined androgen blockade with leuprorelin and flutamide had demonstrated no significant differences in time to treatment failure, time to progression, or overall survival (Bono *et al* 1998).

Inclusion of trials using only the UK licensed doses of LHRH analogues provided an unbalanced view as it excluded one of the key Prostap survival outcome trials in which the US licensed dose of Prostap 7.5mg was used (D'Amico *et al* 2004). The equivalence of monthly administration of 3.75mg and 7.5mg leuprorelin had been demonstrated by Bischoff *et al* (1990). In addition, D'Amico *et al* was referred to in the Prostap summary of product characteristics (SPC). The PMCPA had previously accepted the use of data from studies that also included doses or dose regimens that were outside the UK licence.

The detailed response from AstraZeneca is given below.

The Panel noted that the letter in question, headed 'Zoladex (goserelin) price reduction from 1st October 2010', was sent to alert readers to a 12% price reduction for Zoladex 10.8mg and that Zoladex 3.6mg continued to be the least expensive one-month LHRHa. The claim at issue appeared in the second paragraph which read 'In addition to the savings Zoladex has demonstrated survival benefits in all 3 stages of prostate cancer (localised, locally advanced and metastatic). *No other LHRHa* has demonstrated survival benefits in all 3 stages of prostate cancer'. In the Panel's view, readers would assume that, the claim referred to the use of Zoladex, and any other LHRHa, as a single agent. The claim was referenced to the Zoladex 3.6mg SPC and to AstraZeneca data on file. The data on file were the results of an August 2008 search for survival data for leuprolide or triptorelin in prostate cancer. Randomized controlled clinical trials and comparisons of a single LHRHa at UK licensed doses with alternative standard therapies were included. Comparisons between different doses or formulations of the same active ingredient, trials of combined androgen blockade and abstracts/ conference proceedings were excluded. No valid randomized controlled trials for leuprorelin were found in any stage of prostate cancer.

A chart of randomized controlled clinical trials with survival endpoints at UK licensed doses comparing features of, *inter alia*, Zoladex and leuprorelin was immediately beneath the claim at issue. The features compared in the chart were whether the products' licences covered metastatic (advanced) prostate cancer; locally advanced prostate cancer, as an alternative to surgical castration; high risk localised or locally advanced prostate cancer, as a adjuvant to radiotherapy; high risk localised or locally advanced prostate cancer, as a neoadjuvant before radiotherapy and locally advanced high-risk prostate cancer at high risk for disease progression, as an adjuvant to radical prostatectomy. The total number of randomized clinical trials were given for each product; there were 11 for Zoladex and none for leuprorelin. Beneath the chart it was stated that the randomized clinical trials were of the UK dose comparing LHRHa monotherapy with a standard comparator therapy and that trials of combined androgen blockade were omitted.

The Panel noted that there was a difference in the clinical particulars listed in the SPCs for Zoladex and Prostap. The Zoladex SPC stated that survival benefit had been shown for Zoladex in metastatic, locally advanced, high-risk localised or locally advanced and locally advanced at high risk of disease progression prostate cancers. There was no similar reference to survival benefits in the Prostap SPCs. The Prostap 3.75mg SPC referred to an advantage for Prostap in relation to mean survival time in metastatic prostate cancer. In patients with metastatic disease no statistically significant difference in survival was found for patients treated with LHRH analogues compared with orchidectomy treatment.

The Prostap 3.75mg SPC referred to disease-free survival and overall survival when leuprorelin 7.5mg/month was used in combination with flutamide. The SPC stated that the higher dose was therapeutically equivalent to the European licensed dose. The SPC stated that there were no disease-free survival data or survival data for leuprorelin when used after prostatectomy in selected patients considered at high risk of disease progression. Similar statements appeared in the Prostap 11.25mg SPC.

The Panel noted that there was no footnote to the claim at issue. It was referenced to the Zoladex SPC and to an inhouse literature search but was not qualified by a footnote thus there could be no breach of the Code in this regard.

The Panel examined the data provided by both parties and considered that although Takeda had survival data from studies that had included leuprorelin, it did not have data to demonstrate survival benefits in all three stages of prostate cancer for Prostap when used as monotherapy.

The Panel thus did not consider that the claim at issue was misleading or that it failed to reflect the totality of the evidence. The claim appeared to reflect the differences in the SPCs for monotherapy with Zoladex compared with Prostap. The claim was in the context of the cost advantage for Zoladex. The Panel did not consider that the comparison was misleading as alleged. No breach of the Code was ruled.

The Panel did not consider that it was misleading *per se* to limit the trials to those using the UK licensed dose. The Panel noted Takeda's concern that this had excluded a study in which leuprorelin 7.5mg had been used. In that regard the Panel noted Takeda's submission that 3.75mg and 7.5mg leuprorelin had been shown to be equivalent. However, the objective of D'Amico *et al* was to assess the survival benefit of radiation therapy alone or in combination with 6 months of androgen suppression therapy in patients with clinically localised prostate cancer. All 98 patients on androgen suppression therapy received flutamide, ten also received goserelin and 88 received leuprorelin. There was no separate analysis of patients taking leuprorelin vs those taking goserelin.

In the Panel's view, for the purposes of the claim at issue, there were problems in using the data from D'Amico *et al* other than the fact that a dose of Prostap was used which was not within the UK licence. The Panel thus did not consider it unreasonable for the results of this study to be disregarded. Similarly the Panel did not consider it unreasonable to exclude the results of another study which used a 1mg dose of Prostap which was not in line with the UK licensed dose. The Panel did not consider that, in the circumstances, it was misleading to refer only to trials using the UK licensed dose. Thus it ruled no breach of the Code.

Takeda UK Ltd complained about a letter (ref CZ004482-ZOLA) about Zoladex (goserelin) sent by AstraZeneca UK Limited to NHS budgetary stakeholders including primary care trust pharmacists, practice managers and other payers. It was sent to medical information sources such as EMIS, BNF and MIMS, the Department of Health and other purchasing organisations and used with appropriate health professionals including oncologists, urologists, GPs and practice nurses. The letter, headed 'Zoladex (goserelin) price reduction from 1st October 2010,' was signed by a member of the AstraZeneca finance department. Inter-company dialogue had settled all but one of the points at issue. Takeda supplied Prostap (leuprorelin).

Goserelin and leuprorelin were both luteinising hormone releasing hormone analogues (LHRHa) indicated for the treatment of prostate cancer.

COMPLAINT

Takeda alleged that the use of the claim: 'No other LHRHa has demonstrated survival benefit in all 3 stages of prostate cancer' was in breach of the following clauses of the Code:

- Clause 7.2, as it was not balanced or accurate, and allowed undue emphasis
- Clause 7.3, as it was misleading
- Clause 7.10, as it was all-embracing

Further in Takeda's view the statement was contrary to the supplementary information to Clause 7, which noted that in general, claims should not be qualified by footnotes and the like.

The claim at issue was an absolute claim based on strict inclusion and exclusion criteria (ie randomized controlled trials of the UK dose comparing LHRHa monotherapy with a standard comparator, combined androgen blockade omitted) and the initial impression of the statement was altered by reading the subsequent footnote. Takeda thus alleged a breach of Clause 7.10.

Takeda believed that the claim presented readers with an exaggerated and unbalanced view of the evidence, and therefore misled by direct implication, as data demonstrated survival benefit in all three stages of prostate cancer with Prostap. In addition, the claim was in bold which allowed undue emphasis. Takeda thus alleged breaches of Clauses 7.2 and 7.3.

The rationale for omitting combined androgen blockade data remained unclear and Takeda alleged that this did not reflect clinical practice and the totality of evidence in terms of the survival benefits offered by Prostap. A long-term study comparing leuprorelin monotherapy vs continuous combined androgen blockade with leuprorelin and flutamide had demonstrated no significant differences in time to treatment failure, time to progression, or overall survival (Bono *et al* 1998) and therefore Takeda alleged that omission of this information was in breach of Clause 7.2.

Inclusion of trials using only the UK licensed doses of LHRH analogues provided an unbalanced view as it excluded one of the key Prostap survival outcome trials in which the US licensed dose of Prostap 7.5mg was used (D'Amico *et al* 2004). The equivalence of monthly administration of 3.75mg and 7.5mg leuprorelin had been demonstrated by Bischoff *et al* (1990). In addition, D'Amico *et al* was referred to in the Prostap summary of product characteristics (SPC). Therefore Takeda believed this constituted a breach of Clause 7.2. Takeda noted that in Case AUTH/1523/10/03 the PMCPA had accepted the use of data from studies that also included doses or dose regimens that were outside the UK licence.

Takeda believed the following data supported evidence of survival benefit for leuprorelin treated patients:

- Two prospective randomized efficacy and safety trials in patients with advanced prostate cancer (ie locally advanced and metastatic disease) which compared the monthly and 3-monthly formulations of leuprorelin, with long-term follow up (43 months) to evaluate median survival time and median time to progression (Wechsel *et al* 1996 and Jocham 1998).

- An open prospective multicentre trial in treatment naïve patients with advanced prostate cancer which evaluated efficacy of leuprorelin 3.75mg in maintaining castrate testosterone levels (which was the accepted surrogate marker for efficacy of hormone therapy) over a 45 month treatment period, inclusive of an evaluation of median survival time and median time to progression (Kienle *et al* 1996).

- A meta-analysis which compared LHRHa therapy to orchiectomy or diethylstilbesterol (DES), in patients with advanced prostate cancer, which supported equivalence in effectiveness among the LHRH analogues (Seidenfeld *et al* 2000).

- A prospective randomized controlled trial of leuprorelin vs DES in advanced prostate cancer. DES had been shown to be equivalent to orchiectomy in terms of overall survival outcomes and was considered the gold standard at the time of publication (Leuprolide Study Group 1984).

- A prospective randomized, controlled trial of leuprorelin as an adjuvant to 3-dimensional conformal radiotherapy (3D-CRT) vs radiotherapy (RT) alone in patients with clinically localised prostate cancer (D'Amico *et al*).

- Two sets of data presented at the American Society of Clinical Oncology (ASCO) in June 2010:

  - A 3 year multicenter, randomized phase III trial comparing a combined modality of leuprorelin and RT with leuprorelin alone in patients with locally advanced prostate cancer (Mottet *et al* 2010) and

  - An intergroup randomized phase III study of androgen deprivation therapy (including leuprorelin among other LHRH analogues) plus RT in locally advanced prostate cancer (Warde *et al* 2010).

Takeda noted that Astra Zeneca failed to include the recently presented data from ASCO in its evidence supporting its claim, which reinforced one of the inherent problems with using categorical comparative claims such as 'No other'. It was the claimant's responsibility to continuously monitor all LHRHa publications to ensure the claim could always be substantiated.

RESPONSE

AstraZeneca strongly denied the claim was in breach of Clauses 7.2, 7.3 and 7.10 as alleged. In particular AstraZeneca did not agree that the claim was not balanced or accurate, allowed undue emphasis, was misleading and all-embracing. AstraZeneca had taken into account all available data in this setting and firmly believed the claim was valid.

AstraZeneca submitted that Zoladex had the largest evidence base of any LHRHa with multiple long-term, randomized-controlled trials demonstrating survival benefit for Zoladex in all three stages of prostate cancer. This body of evidence was unique amongst the LHRH analogues and AstraZeneca noted that Takeda had not challenged the existing Zoladex dataset. Conversely, the studies submitted by Takeda did not support its assertion that Prostap had demonstrated survival benefit in all three stages of prostate cancer.

The fact that Zoladex was the only LHRHa with demonstrated survival benefits in all three stages of prostate cancer was also consistent with the current licences for the LHRH analogues. In relation to this, during a 2008 Medicines and Healthcare products Regulatory Agency (MHRA)-initiated review of the prostate cancer indications for all UK approved gonadorelin analogues, Prostap was granted an amended licence authorizing use in all three stages of prostate cancer. Subsequent to the outcome of the review for Prostap, the MHRA also allowed amended wording in Section 4.1 of the Zoladex SPC to reflect the unique evidence base that goserelin had demonstrated survival benefits in the 3 stages of prostate cancer as outlined above. This was also supported by MHRA correspondence to AstraZeneca around the time of this review:

'We highlighted that no survival claims have been approved in the Prostap SPC, whereas the Zoladex SPC now enjoys a number of new survival claims in early prostate cancer as a result of this review …'.

AstraZeneca submitted that it was thus clear that, when it did its review, the MHRA did not consider that the Prostap dataset supported survival benefit across all three stages of prostate cancer.

The fact that Zoladex had demonstrated survival benefits in all three stages of prostate cancer was also clear from review of the specific wording for the relevant Zoladex licences taken from the indication section of the SPC (emphasis added to illustrate the specific wording):

> 'In the treatment of metastatic prostate cancer where Zoladex has demonstrated comparable survival benefits to surgical castrations (see section 5.1)'.
>
> 'In the treatment of locally advanced prostate cancer, as an alternative to surgical castration where Zoladex has demonstrated comparable survival benefits to an anti-androgen (see section 5.1)'.
>
> 'As adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer where Zoladex has demonstrated improved disease-free survival and overall survival (see section 5.1)'.

Conversely, none of the other SPCs for the available LHRH analogues (ie Prostap, Decapeptyl Gonapeptyl and Vantas) referred to survival benefit across the three stages of prostate cancer. This further supported the claim for Zoladex that 'No other LHRHa has demonstrated survival benefits in all 3 stages of prostate cancer'.

Takeda alleged that the claim 'No other LHRHa has demonstrated survival benefits in all 3 stages of prostate cancer' was contrary to the supplementary information to Clause 7 as it was supported by the use of footnotes. However, the claim in the letter at issue was not qualified by a footnote and therefore AstraZeneca was unclear as to what Takeda had referred.

AstraZeneca denied a breach of Clause 7.10. The claim was carefully considered and worded to accurately reflect the available evidence base; it did not exaggerate the properties of Zoladex, nor could it be considered an all-embracing or superlative claim. Rather the claim was a simple statement of fact and was specific to treatment with LHRH analogues in all three stages of prostate cancer and substantiated with survival endpoint data from numerous randomized clinical trials and a unique licence. AstraZeneca did not agree that data had demonstrated a survival benefit in all 3 stages of prostate cancer with Prostap.

The claim had the words 'No other LHRHa …' printed in bold. Takeda had alleged that this allowed undue emphasis in breach of Clauses 7.2 and 7.3. AstraZeneca did not understand how this placed undue emphasis, but rather appropriate emphasis on the fact that only Zoladex had survival benefit in all three stages of prostate cancer.

AstraZeneca noted Takeda's concerns about the omission of combined androgen blockade data and that the claim did not reflect clinical practice. AstraZeneca stated that combined androgen blockade referred to the use of two medicines simultaneously to treat prostate cancer: an LHRHa (such as Prostap or Zoladex) and an anti-androgen (such as flutamide or bicalutamide). The claim at issue referred to single agent treatment with LHRH analogues and would be interpreted as such by health professionals. Furthermore, in routine clinical practice, combined androgen blockade was not endorsed by the National Institute for Health and Clinical Excellence (NICE) in any of the three treatment settings, and it was specifically not recommended as first line treatment in advanced disease. Therefore, AstraZeneca did not understand how the claim 'No other LHRHa has demonstrated survival benefits in all 3 stages of prostate cancer' could be interpreted as referring to combined androgen blockade, especially since this did not reflect routine clinical practice.

AstraZeneca was not aware of any studies on combined androgen blockade which demonstrated the survival benefit conferred by a single agent. Such combination studies did not allow evidence-based conclusions to be drawn regarding the survival benefit of single agents. Only studies designed to investigate single agents should be used to determine the benefit of the agent under investigation. For example, Takeda cited Bono *et al* as evidence that leuprorelin monotherapy was no different in efficacy from combined androgen blockade (leuprorelin plus flutamide). This was misleading since the study was not designed to show equivalence or non-inferiority, but to look for an advantage for combined androgen blockade (leuprorelin plus flutamide) vs leuprorelin monotherapy. The paper reported that at a cut-off analysis, when mean follow-up period was 43.7 ± (SD) 24.1 months, no statistically significant differences in terms of time to treatment failure, time to progression and death rate were detected. That the paper failed to demonstrate superiority for combined androgen blockade did not prove that leuprorelin monotherapy was equivalent in efficacy as this would require a formal pre-defined equivalence analysis.

Based on the above, AstraZeneca considered that Prostap data relating to combined androgen blockade was not relevant to the validity of the claim in question and therefore the claim was not in breach of Clause 7.2.

The only evidence provided by Takeda to support survival benefit in the localized prostate cancer came from D'Amico *et al*. Takeda claimed that this study assessed radiotherapy plus leuprorelin vs radiotherapy alone. This was factually incorrect and misleading on two counts:

- The investigational arm in the study allowed inclusion of patients on any LHRHa and of the 98 patients, 10 were on Zoladex rather than leuprorelin. Therefore this study could not demonstrate survival benefit specifically for leuprorelin.

- The study combined two active treatments in the investigational arm: flutamide in combination with either leuprorelin or goserelin. Therefore the study could not identify the relative contributions of each active treatment to survival benefit. Indeed the study itself concluded: '… the question of whether complete (LHRH agonist and nonsteroidal anti-androgen) compared with partial androgen blockade (LHRH agonist) is necessary to achieve the survival benefit noted in our study remains'. The authors had themselves concluded that the study was unable to determine whether the benefit came from flutamide or from the LHRHa.

Therefore, consistent with AstraZeneca's knowledge of the literature, Takeda had not submitted any evidence that Prostap had demonstrated survival benefit in localised prostate cancer. AstraZeneca was concerned that Takeda considered D'Amico as 'one of the key Prostap survival outcome trials'.

Takeda had stated that the exclusion of D'Amico *et al* from being referenced in the claim provided an unbalanced view. However, as stated above, AstraZeneca did not accept that this study, irrespective of the dose used, supported the conclusion that Prostap had demonstrated survival benefit in localised prostate cancer. Furthermore, the fact that this study was referred in the SPC for Prostap was not relevant to concluding that Prostap had demonstrated survival benefit in localised prostate cancer. AstraZeneca referred again to the statement in the letter from the MHRA. Therefore, AstraZeneca did not agree that the claim at issue was in breach of Clause 7.2.

AstraZeneca stated that in general, the additional studies referred to by Takeda were small and limited in the conclusions that could be drawn from them. Nevertheless, AstraZeneca had reviewed each in turn to explain why they did not provide evidence for survival benefits for Prostap in all three stages of prostate cancer.

Localised prostate cancer:

No survival data for Prostap had been submitted by Takeda in this phase of prostate cancer. AstraZeneca referred to its comments above on D'Amico *et al*.

The fact that Takeda had no data to support survival benefit in this stage of prostate cancer supported AstraZeneca's position that the dataset for Prostap did not invalidate the claim 'No other LHRHa has demonstrated survival benefits in all 3 stages of prostate cancer'.

Locally advanced prostate cancer:

Takeda had outlined three studies that it considered demonstrated survival benefits for Prostap in locally advanced disease. Each of these had been reviewed in turn: Jocham was considered in the section for advanced prostate cancer below and the two sets of data from ASCO were considered here (Warde *et al* and Mottet *et al*). AstraZeneca noted Takeda's concern that AstraZeneca failed to refer to recently presented data from ASCO. In AstraZeneca's view, the data provided by Takeda from ASCO (Warde *et al* and Mottet *et al*) were not relevant to this complaint. However, for completeness, these two studies were outlined here.

Warde *et al* was a well conducted, randomized, controlled, phase III study designed to evaluate whether adding radiotherapy to an LHRHa was beneficial for patient outcomes. The authors concluded that the addition of radiotherapy was of value to patients. The study did not measure the impact of leuprorelin on survival. Furthermore, in order to lower testosterone levels, the study allowed inclusion of any LHRHa or orchiectomy (removal of both testes) as baseline therapy and therefore could not be used to demonstrate survival benefit of leuprorelin.

Mottet *et al* evaluated the benefit of adding radiotherapy to leuprorelin vs leuprorelin alone. Although this had only been published in abstract form no survival data were presented by the authors, and the design of the study aimed to evaluate the benefit of adding radiotherapy to LHRHa and not to assess the survival benefit of Prostap monotherapy.

Advanced/metastatic prostate cancer:

Jocham was a single arm study of 37 patients who were followed up long-term following exit from a larger study. As Takeda indicated, this study recruited patients with both locally advanced and metastatic disease and therefore could not separate the survival outcomes for the two disease settings. Although the paper reported a survival time, this was a single arm study that therefore could not be used to demonstrate survival benefit. The paper made indirect comparisons of survival based on these results. However, AstraZeneca did not consider that this data was robust enough to make indirect comparisons across studies to suggest that a survival benefit existed for Prostap in this stage of prostate cancer.

Wechsel *et al* looked at two different formulations of leuprorelin (1 month vs 3 month) thus AstraZeneca failed to see how this could provide evidence of survival benefits for leuprorelin over a comparator.

Kienle *et al* was a small, non-randomized study of leuprorelin monotherapy vs a combination of leuprorelin and an anti-androgen. The study evaluated the benefit of anti-androgens to the treatment of advanced disease and demonstrated that adding an anti-androgen appeared to shorten survival. However the authors noted that the study was not randomized and therefore worse prognosis patients received combined treatment from the start and this potentially explained the poorer survival seen in this group. In any case this study was unable to demonstrate a survival benefit of leuprorelin as it was designed to measure the impact of the addition of an anti-androgen.

Seidenfeld *et al* was a systematic review of studies in advanced/metastatic disease. Ten LHRHa studies were identified including five with goserelin. Only one study of leuprorelin was identified at a dose of 1mg subcutaneous daily (the licensed dose was 3.75mg monthly). Takeda had referred to this trial (Leuprolide Study Group) as evidence of survival benefit. AstraZeneca was concerned that Takeda would use an unapproved dose of leuprorelin (and one that was unavailable in the UK) to refute a survival benefit claim for Zoladex. Although the Prostap SPC referred to equivalence of 3.75mg and 7.5mg, it did not refer to a 1mg dose of leuprorelin, which therefore remained off licence. Furthermore it would be inappropriate, due to patient safety, to infer 1mg/day (up to 31mg/month) of leuprorelin was equivalent to 3.75mg/month in the absence of any supporting data.

With regard to other supporting information, AstraZeneca submitted that during the development of the prostate cancer guidelines, the National Institute for Health and Clinical Excellence (NICE) assessed the body of survival evidence in locally advanced disease and cited a Cochrane review (Kumar *et al* 2006). Kumar *et al* cited a number of published studies which they assessed during their evaluation. There were no leuprorelin data referenced within this review, although there were two large randomized studies of Zoladex. This further emphasized AstraZeneca's assertion that no survival benefit evidence existed for Prostap in locally advanced disease. This position was consistent with the Cochrane review.

In addition, in 2010 a well recognized review body, the Midlands Therapeutics Review and Advisory Committee (MTRAC) produced a commissioning support document for Prostap. This document aimed to supersede the 2008 document which did not recommend Prostap stating a lack of evidence. The 2010 document supported the use of Prostap but stated: 'No relevant studies were identified using leuprorelin as an alternative to surgical castration in locally advanced prostate cancer, or as adjuvant therapy with either radiotherapy or prostatectomy'.

The Prostap SPC contradicted Takeda's assertion that Prostap had demonstrated survival benefit in all three stages of prostate cancer. Section 5.1 of the Prostap SPC stated '… The use of a LHRH agonist may be considered after prostatectomy in selected patients considered at high risk of disease progression. There are no disease free survival data or survival data with leuprorelin in this setting' (emphasis added).

In summary, AstraZeneca firmly believed that there was a substantial evidence base for Zoladex which demonstrated survival benefit in all three stages of prostate cancer. This was consistent with the specific licence wording, clinical trial data, clinical guidelines, systematic reviews and local formulary assessments. The position had been recognized by the MHRA in the unique range of licensed indications granted for Zoladex which underpinned the claim at issue. In contrast Prostap and all other LHRH analogues lacked evidence to demonstrate survival benefit across all three stages of prostate cancer.

AstraZeneca acknowledged that leuprorelin was an effective treatment for patients with prostate cancer. This was supported by many clinical guidelines, formularies, and current clinical practice and was based on its data for testosterone suppression. However this did not invalidate the claim for Zoladex that 'No other LHRHa has demonstrated survival benefits in all 3 stages of prostate cancer'. It remained the case that only Zoladex had such data. AstraZeneca was concerned that Takeda had considered that the studies above demonstrated survival benefits for Prostap across all 3 stages of prostate cancer (whether at unlicensed doses, in non- randomized studies or in studies assessing other active agents). These studies did not support survival benefit for Prostap across all three stages of prostate cancer and therefore did not invalidate the claim at issue.

AstraZeneca denied that the claim was in breach of Clauses 7.2 or 7.3. In addition, the claim was neither exaggerated nor all embracing; AstraZeneca denied the alleged breach of Clause 7.10.

PANEL RULING

The Panel noted that the letter in question, headed 'Zoladex (goserelin) price reduction from 1st October 2010', was sent to alert readers to a 12% price reduction for Zoladex 10.8mg and that Zoladex 3.6mg continued to be the least expensive one-month LHRHa. The claim at issue appeared in the second paragraph which read 'In addition to the savings Zoladex has demonstrated survival benefits in all 3 stages of prostate cancer (localised, locally advanced and metastatic). **No other LHRHa** has demonstrated survival benefits in all 3 stages of prostate cancer'. In the Panel's view, readers would assume that, given the purpose of the letter and the context in which the claim appeared, that the claim referred to the use of Zoladex, and any other LHRHa, as a single agent. The claim was referenced to the Zoladex 3.6mg SPC and to AstraZeneca data on file. The data on file were the results of an August 2008 EMBASE and MEDLINE search for survival data for leuprolide or triptorelin in prostate cancer. The inclusion criteria were randomized controlled clinical trials and comparisons of a single LHRHa at UK licensed doses with alternative standard therapies. The three exclusion criteria were: comparisons between different doses or formulations of the same active ingredient, trials of combined androgen blockade and abstracts/conference proceedings. No valid randomized controlled trials for leuprorelin were found in any stage of prostate cancer and no survival benefit data were found regarding the use of triptorelin in high risk localised prostate cancer.

The claim at issue was not referenced to a footnote as stated by Takeda. A chart of randomized controlled clinical trials with survival endpoints at

UK licensed doses comparing features of Zoladex, leuprorelin and triptorelin was immediately beneath the claim at issue. The features compared in the chart were whether the products' licences covered metastatic (advanced) prostate cancer; locally advanced prostate cancer, as an alternative to surgical castration; high risk localised or locally advanced prostate cancer, as a adjuvant to radiotherapy; high risk localised or locally advanced prostate cancer, as a neoadjuvant before radiotherapy and locally advanced high-risk prostate cancer at high risk for disease progression, as an adjuvant to radical prostatectomy. The total number of randomized clinical trials were given for each product; there were 11 for Zoladex, none for leuprorelin and 3 for triptorelin. Beneath the chart it was stated that the randomized clinical trials were of the UK dose comparing LHRHa monotherapy with a standard comparator therapy and that trials of combined androgen blockade were omitted.

The Panel noted that there was a difference in the clinical particulars listed in the SPCs for Zoladex and Prostap. Section 4.1, Therapeutic indications, of the Zoladex SPC stated that survival benefit had been shown for Zoladex in metastatic, locally advanced, high-risk localised or locally advanced and locally advanced at high risk of disease progression prostate cancers. There was no reference to survival benefits in the indication section of the Prostap SPCs. Section 5.1 of the Prostap 3.75mg SPC referred to an advantage for Prostap in relation to mean survival time in metastatic prostate cancer. In patients with metastatic disease no statistically significant difference in survival was found for patients treated with LHRH analogues compared with orchidectomy treatment.

The Prostap 3.75mg SPC referred to disease-free survival and overall survival when leuprorelin 7.5mg/month was used in combination with flutamide. The SPC stated that the higher dose was therapeutically equivalent to the European licensed dose. The SPC stated that there were no disease-free survival data or survival data for leuprorelin when used after prostatectomy in selected patients considered at high risk of disease progression.

Similar statements appeared in the Prostap 11.25mg SPC.

With regard to the alleged breach of Clause 7.10, the Panel noted that there was no footnote to the claim at issue. It was referenced to the Zoladex SPC and to an inhouse literature search but was not qualified by a footnote. As there was no footnote there could be no breach of the Code in this regard. Thus the Panel ruled no breach of Clause 7.10.

The Panel noted AstraZeneca's comments about Wechsel *et al*. The study was designed to compare the efficacy, safety and tolerability of the two formulations of Prostap (3.75mg monthly or 11.25mg monthly) and to investigate whether they were able to lower testosterone effectively and persistently to the castrate level in the same way. The patients all had a life expectancy of >12 months; the study only lasted for 9 months. The authors stated that in relation to long-term prognosis, the reduction in prostate-specific antigen (PSA) might be regarded as clinically very important. There was no direct mention of survival benefits in this study.

The Panel examined the data provided by both parties and considered that although Takeda had survival data from studies that had included leuprorelin, it did not have data to demonstrate survival benefits in all three stages of prostate cancer for Prostap when used as monotherapy.

The Panel thus did not consider that the claim at issue was misleading or that it failed to reflect the totality of the evidence. The claim appeared to reflect the differences in the SPCs for monotherapy with Zoladex compared with Prostap. The claim was in the context of the cost advantage for Zoladex. The Panel did not consider that the comparison was misleading as alleged. No breach of Clauses 7.2 and 7.3 were ruled.

The Panel did not consider that it was misleading *per se* to limit the trials to those using the UK licensed dose. The Panel noted Takeda's concern that this had excluded the results of D'Amico *et al* in which a dose of 7.5mg leuprorelin had been used. In that regard the Panel noted Takeda's submission that 3.75mg and 7.5mg leuprorelin had been shown to be equivalent. However, the objective of D'Amico *et al* was to assess the survival benefit of radiation therapy alone or in combination with 6 months of androgen suppression therapy in patients with clinically localised prostate cancer. All 98 patients on androgen suppression therapy received flutamide, ten also received goserelin and 88 received leuprorelin. There was no separate analysis of patients taking leuprorelin vs those taking goserelin.

In the Panel's view, for the purposes of the claim at issue, there were problems in using the data from D'Amico *et al* other than the fact that a dose of Prostap was used which was not within the UK licence. The Panel thus did not consider it unreasonable for the results of this study to be disregarded. Similarly the Panel did not consider it unreasonable to exclude the results of the Leuprolide Study Group because the Prostap dose used, 1mg daily, was not in line with the UK licensed dose. The Panel did not consider that, in the circumstances, it was misleading to refer only to trials using the UK licensed dose. Thus it ruled no breach of Clause 7.2.

Complaint received **28 February 2011**

Case completed **5 May 2011**

CASE AUTH/2392/2/11

ANONYMOUS v SANOFI-AVENTIS

Conduct of representative

An anonymous complainant raised concerns about the attendance of patients at a Multaq (dronedarone) promotional meeting organised by a Sanofi-Aventis representative. During the meeting patients took part in a presentation given by a consultant cardiologist. The complainant considered that it was inappropriate for the representative to pay for two of the patients to eat at the restaurant, after the presentation, attended by many health professionals. That aside, the complainant believed that the meeting was well managed and most informative.

The detailed response from Sanofi-Aventis is given below.

The Panel considered that the patient perspective might be a useful component of some pharmaceutical company meetings. If patients were to speak however, the company must ensure that all of the arrangements complied with the Code. Patients would, in effect, be speaking on the company's behalf and in that regard they should be adequately briefed with regard to the requirements of the Code. Companies should not allow those they had engaged as speakers to informally invite others to speak.

The Panel noted Sanofi-Aventis' submission that the representative was told two days before the meeting that the consultant had thought of inviting some patients to the meeting. At that stage the representative should have either asked the consultant not to invite the patients or taken steps to prepare for their possible attendance and to ensure compliance with the Code in that regard. From Sanofi-Aventis' submission it did not appear that the representatives had done either. When a patient and his wife stayed for the meal the representatives assumed that the consultant had invited them to do so. This was unacceptable; it was beholden upon the representatives to remain in control of all of the meeting arrangements.

The fact that patients attended a meeting where Sanofi-Aventis' medicine was being promoted meant that Sanofi-Aventis had promoted a prescription only medicine to the public. Thus the Panel ruled a breach as acknowledged by Sanofi-Aventis.

The Panel considered that in their organization of the meeting the representatives had not maintained a high standard of ethical conduct or complied with the Code. A breach was ruled.

The Panel noted that as speakers and a carer at the meeting it was not unreasonable that the members of the public should be compensated in some way for giving up their own time to provide a service to the company. Any payment or recompense should adequately reflect the time and effort involved. The Panel noted that the meeting was a promotional meeting for health professionals and so any associated hospitality should not extend beyond those qualified to attend the meeting in their own right. In that regard, the members of the public did not qualify as proper delegates to the meeting.

It could be argued that as speakers the members of the public were participants at the meeting as meant by the supplementary information to the Code. The Panel did not consider that it was necessarily unacceptable for a patient speaker to receive hospitality providing that the hospitality complied with the Code and there was no promotion of prescription only medicines. In that regard the Panel noted Sanofi-Aventis's submission that neither representative had any recollection of a product being discussed at the meal. The Panel also noted its ruling of a breach of the Code. The Panel considered that taking all the circumstances into account the provision of the meal to the patient and his carer in itself was not unacceptable. No breach of the Code was ruled.

With regard to high standards the Panel considered that the matter was covered by its ruling of a breach of the Code above and thus ruled no breach of the Code. The Panel was concerned that the representatives' unprofessional handling of the meeting might have given a poor impression, particularly to the patient and his wife who stayed for the meal. Nonetheless, the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

An anonymous, contactable complainant raised concerns about the attendance of patients at a promotional meeting organised by Sanofi-Aventis.

The complaint was considered under the Constitution and Procedure for the 2011 Code in relation to the requirements of the 2008 edition of the Code.

COMPLAINT

The complainant noted that a medical representative at Sanofi-Aventis had organised a promotional meeting at a restaurant in November 2010. During the meeting it was made evident that four patients were in attendance and took part in a presentation given by a consultant cardiologist. The complainant was concerned that the representative

paid for two of the patients to eat at the restaurant, after the presentation, attended by many health professionals. The complainant considered that this was inappropriate behaviour for a medical representative. The complainant believed that the meeting was well managed and most informative but considered that paying for a patient to enjoy a meal within the room where a medical presentation was conducted was entirely inappropriate.

When writing to Sanofi-Aventis the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2, 19.1, and 22.1 of the 2008 edition of the Code.

RESPONSE

The meeting was arranged by two Sanofi-Aventis representatives in conjunction with a consultant cardiologist from the local hospital. The subject of the meeting was 'New advances in atrial fibrillation management'; a copy of the invitation sent to invitees was provided. In line with company policy, the consultant cardiologist had signed a standard speaker agreement, a copy of which was also provided. The restaurant was booked based on its suitability for this sort of meeting as it had a private room away from the main restaurant. The representative pre-ordered 40 set meals based on the expected attendance.

Two days before the meeting the consultant cardiologist mentioned to the representative that he had thought of inviting some patients to the meeting to give a patient perspective on the disease; at this point he had not invited them. On the evening of the meeting the consultant cardiologist told the representatives that he had invited two of the patients he had seen in clinic that morning to come along and speak on their experience of atrial fibrillation from the perspective of a patient.

On the evening of the meeting three members of the public were present; two patients as speakers, and the wife of one of the patients who attended as a carer.

The consultant cardiologist spoke for approximately 1 hour 15 minutes, a copy of his slides were provided. He then asked the two patients to speak and they spoke for approximately 10 minutes explaining their experiences of atrial fibrillation and its impact on their lives.

At the end of the presentations the two representatives sorted out the seating etc for the meal; neither of them spoke to the members of the public at this time. During the meal the representatives circulated and talked to the different attendees, neither representative had any recollection of a product being discussed during the meal as a significant amount of product discussion had already taken place. The patient who had arrived on his own had left at this point but the other patient and his wife stayed and ate with the other attendees of the meeting. Neither of the representatives asked the members of the public to stay to eat and both assumed that the consultant who invited them to speak had done so.

A copy of the call record for the meeting along with copies of the expense claim and receipt for the hospitality were provided. The hospitality was a set meal for 40 people along with drinks charged as ordered.

Sanofi-Aventis accepted that technically the arrangements for this meeting breached Clause 22.1 in that patients were present during a promotional meeting. It did not accept that it was inappropriate to provide hospitality to the members of the public as they had acted as bona fide speakers relevant to the content of the meeting, and as such were present in this capacity rather than as lay persons and the timing of the meeting was such that offering subsistence was appropriate. However, all other arrangements fell within the Code. Therefore the company denied any breach of Clauses 2, 9.1, 15.2 or 19.1.

PANEL RULING

The Panel noted that it was not clear whether the complainant had attended the meeting at which the two patients had presented.

The Panel considered that the patient perspective might be a useful component of some pharmaceutical company meetings. If patients were to speak at a meeting however, the pharmaceutical company must ensure that all of the arrangements complied with the Code. In the Panel's view the patients would, in effect, be speaking on the company's behalf and in that regard they should be adequately briefed with regard to the requirements of the Code. Companies should not allow those they had engaged as speakers to informally invite others to speak.

The Panel noted Sanofi-Aventis' submission that the representative was told two days before the meeting that the consultant had thought of inviting some patients to the meeting. At that stage the representative should have either asked the consultant not to invite the patients or taken steps to prepare for their possible attendance and to ensure compliance with the Code in that regard. From Sanofi-Aventis' submission it did not appear that the representatives had done either. When the patient and his wife stayed for the meal the representatives assumed that the consultant had invited them to do so. This was unacceptable; it was beholden upon the representatives to remain in control of all of the meeting arrangements.

The Panel noted that the slides used by the consultant promoted Sanofi-Aventis' product Multaq (dronedarone).

Clause 22.1 prohibited the advertising of prescription only medicines to the public. The fact that patients attended a meeting where Sanofi-Aventis' medicine was being promoted meant that

Sanofi-Aventis had promoted a prescription only medicine to the public. Thus the Panel ruled a breach of Clause 22.1 as acknowledged by Sanofi-Aventis.

The Panel considered that in their organization of the meeting the representatives had not maintained a high standard of ethical conduct or complied with the Code. A breach of Clause 15.2 was ruled.

Sanofi-Aventis submitted a list of 40 health professional attendees. Sanofi-Aventis did not appear to have a record of the 2 patients and 1 spouse that attended the meeting. The Panel did not know how many health professionals had attended the meal. The Panel noted that the representatives had pre-ordered 40 set meals at a cost of £22.24 per head. Drinks had cost £185.70.

The Panel noted that as speakers and a carer at the meeting it was not unreasonable that the members of the public should be compensated in some way for giving up their own time to provide a service to the company. Any payment or recompense should adequately reflect the time and effort involved. The Panel noted that the meeting was a promotional meeting for health professionals and so any associated hospitality should not extend beyond those qualified to attend the meeting in their own right. In that regard, the members of the public did not qualify as proper delegates to the meeting.

It could be argued that as speakers the members of the public were participants at the meeting as meant by the supplementary information to Clause 19.1, Meetings and hospitality. The Panel did not consider that it was necessarily unacceptable for a patient speaker to receive hospitality providing that the hospitality complied with the Code and there was no promotion of prescription only medicines. In that regard the Panel noted Sanofi-Aventis's submission that neither representative had any recollection of a product being discussed at the meal. The Panel also noted its ruling of a breach of Clause 22.1. The Panel considered that taking all the circumstances into account the provision of the meal to the patient and his carer in itself was not unacceptable. No breach of Clause 19.1 was ruled.

With regard to Clause 9.1 the Panel considered that the matter was covered by its ruling of a breach of Clause 15.2 and thus ruled no breach of Clause 9.1. The Panel was concerned that the representatives' unprofessional handling of the meeting might have given a poor impression of the industry, particularly to the patient and his wife who stayed for the meal. Nonetheless, the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

Complaint received **28 February 2011**

Case completed **28 April 2011**

CASE AUTH/2393/3/11

VOLUNTARY v ADMISSION BY BAXTER

Failure to take the ABPI Medical Representatives Examination within first year

Baxter advised the Authority that a review of training records showed that 21 of its representatives had not taken the ABPI Medical Representatives Examination in their first year of such employment. The one year period had already expired. In accordance with the Constitution and Procedure for the Prescription Medicines Code of Practice Authority, the Director treated the matter as a complaint.

Baxter submitted that the situation had been complicated by the change in status of some roles, changes in reporting structure and the acquisition of another company, however the Code was clear on what was required. Those concerned had been told that they must take their respective ABPI examinations by the end of June 2011 or their continued employment with the company might be at risk. Baxter would audit its internal training record more often to ensure that this could not happen again.

The detailed admission and response from Baxter is given below.

The Panel noted that the only issue to be determined was whether representatives had taken the examination in their first year of employment as a representative. The Panel did not have any information about the roles of the employees prior to joining Baxter.

The Panel noted that Baxter had highlighted the employment status of 17 employees, 7 of whom had previously been employed by a company acquired by Baxter in September 2009. None of the 17 employees had sat their examination in the first year of employment with Baxter although 4 had sat the examination within two years: 1 had passed, 1 had partially passed and was booked to resit failed papers, and two were awaiting results. Of the remaining 13 employees, 12 were scheduled or hoped to sit the examination by September 2011, and 1 had been ill and unable to register.

The Panel noted that Baxter considered that the ABPI Medical Representatives Examination was appropriate for a wide range of its employees. In the Panel's view only those who satisfied the definition and role of a representative were required under the Code to take the examination. A company might decide to require others to sit the examination but it was not a breach of the Code if they failed to do so.

Baxter had only provided the job titles of the 17 employees. Five clearly had a sales role. One specialist nurse had an entirely clinical non-promotional role. The company had also decided to require other clinical and training nurses who were occasionally part of promotional meetings to sit the examination.

The Panel ruled that in relation to those individuals whose role and responsibilities satisfied those of a representative as set out in the Code, there had been a breach of the Code in relation to their failure to sit the examination in the first year of their employment.

Baxter Healthcare Ltd advised the Authority that some of its representatives had not taken the ABPI Medical Representatives Examination in their first year of such employment. The one year period had already expired.

In accordance with Paragraph 5.6 of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority, the Director treated the matter as a complaint.

COMPLAINT

Baxter stated that a review of training records showed that 21 of its sales representatives in Great Britain and Northern Ireland had not taken the examination within their first year of that role.

This situation had been complicated by the change in status of some roles, changes in reporting structure and the acquisition of another company, however the Code was clear on what was required.

Given the seriousness of this case, those concerned had been told that they must take their respective ABPI examinations by the end of June 2011, or as per the terms of their employment contracts, their continued employment with the company might be at risk.

Baxter formally requested an extension in the case of these individuals, subject to the time limit stated above.

Baxter would audit its internal training record more often to ensure that this could not happen again.

When writing to Baxter, the Authority asked it to respond in relation to Clause 16.3 of the Code.

RESPONSE

Baxter provided a spread sheet of employees, their respective examination dates and any comments as appropriate. On more detailed review, Baxter had found that there were seventeen employees

involved; three had taken the examination already (one had passed and two were awaiting their results) and all others were currently studying.

Baxter noted that it had initially asked for an extension until 30 June 2011, to allow its identified employees to register and prepare for examinations. Baxter noted that from the spread sheet provided all identified employees (except in Northern Ireland) were registered for examinations before that date.

The matter had come to light when one of Baxter's employees informed the company that they could not register for their ABPI examination because they were out of time. Baxter audited all employees to ensure this was not a problem with others too. Having identified a number of shortfalls, Baxter immediately communicated with respective managers to ensure their employees started their ABPI examination process, revised its policy and tracking documentation and advised the Authority of its concern.

Baxter's ABPI Policy was provided, including its internal process document regarding the ABPI examination. From this it would be seen that Baxter had put additional measures in place that would avoid this situation in future. Baxter submitted that its Offer of Employment and Job Change templates showed that it formally considered the requirement and status of the ABPI examination at key times of change in employment (copies were provided). Since Baxter had been a member of the ABPI, the ABPI examination had been included in its contracts of employment as a condition of employment, and this would continue to be the case; the only exception was in Ireland, where this would now be added to employment contracts. This policy had been shared with all senior management and was on Baxter's intranet.

It only became apparent through discussions and internal reorganisation that Baxter's colleagues from Ireland who worked in Northern Ireland would need to attain the ABPI qualification. For these individuals, although they worked primarily in the Republic of Ireland with only some of their activities occurring in Northern Ireland, Baxter had included them in its ABPI process. They had already attended a workshop to prepare for their examinations. They were keen to register for examinations, however were currently unable to do so; if they entered a start date of more than two years ago they received a warning message and were prevented from registering. Baxter asked how it might remedy this situation, as it had communicated that they would need to take these examinations as a priority.

Although Baxter clinical and training nurses were not sales representatives *per se*, Baxter recognised that occasionally they were in promotional situations and so Baxter was committed to them also successfully completing the ABPI examination. These employees were indicated within the spread sheet.

Baxter noted that it used a distance learning platform for the ABPI; every employee, regardless of their role, had access to them as part of Baxter's commitment to continuous learning. A number of employees listed on the spread sheet had already completed their training regarding the 2011 update.

Baxter apologised that it found itself in these unfortunate circumstances. Additional measures had been put in place to avoid this happening again.

PANEL RULING

The Panel noted that Clause 16.3 stated that representatives must pass the appropriate ABPI representatives' examination. They must take the appropriate examination within their first year of such employment. Prior to passing the appropriate examination, they might be engaged in such employment for no more than two years, whether continuous or otherwise. The relevant supplementary information gave the Director discretion to grant an extension in the event of failure to comply with either time limit subject to the representative taking or passing the examination within a reasonable time.

The Panel noted that the only issue to be determined was whether representatives had taken the examination in their first year of employment as a representative. The Panel did not have any information about the roles of the employees prior to joining Baxter.

The Panel noted that Baxter had highlighted the employment status of 17 employees, 7 of whom had previously been employed by a company acquired by Baxter in September 2009. None of the 17 employees had sat their examination in the first year of employment with Baxter although 4 had sat the examination within two years: 1 had passed, 1 had partially passed and was booked to resit failed papers, and two were awaiting results. Of the remaining 13 employees, 9 were scheduled to sit the examination between April and September 2011, 3 were unable to register but hoped to sit the examination in September 2011 and 1 had been ill and unable to register.

The Panel noted that a representative was defined in Clause 1.6 of the Code as someone who called on members of the health professions and administrative staff in relation to the promotion of medicines. In the Panel's view such people would often have job titles other than 'representative'. The term promotion was defined in Clause 1.2 as any activity undertaken by a pharmaceutical company or with its authority which promoted the prescription, supply, sale or administration of its medicines. Clause 16.4 stated that the ABPI Medical Representatives Examination must be taken by representatives whose duties comprised or included one or both of calling upon, inter alia, doctors and/or other prescribers; and/or the promotion of medicines on the basis of their particular therapeutic properties.

The Panel noted that Baxter considered that the ABPI Medical Representatives Examination was appropriate for a wide range of its employees. In the Panel's view only those who satisfied the definition and role of a representative, as set out above, were required under the Code to take the examination. A company might decide to require others to sit the examination but it was not a breach of the Code if they failed to do so.

Baxter had only provided the job titles of the 17 employees. Five clearly had a sales role. One specialist nurse had an entirely clinical non-promotional role. The company had also decided to require other clinical and training nurses who were occasionally part of promotional meetings to sit the examination.

The Panel ruled that in relation to those individuals whose role and responsibilities satisfied those of a representative as set out in the Code (Clauses 1.6 and 16.4), there had been a breach of Clause 16.3 in relation to their failure to sit the examination in the first year of their employment.

Complaint received **23 March 2011**

Case completed **20 April 2011**

BOEHRINGER INGELHEIM v LUNDBECK and TEVA

Promotion of Azilect

Boehringer Ingelheim complained about joint activities undertaken by Lundbeck and Teva at a World Parkinson's congress to support Azilect (rasagiline). The congress was attended by health professionals and patients.

The detailed responses from Lundbeck and Teva are given below.

Boehringer Ingelheim noted that all delegate bags, including those of patients, contained an invitation to a Lundbeck/Teva satellite symposium entitled 'Slowing disease progression in Parkinson's disease' which in Boehringer Ingelheim's view implied that attendees would hear about a medicine to slow Parkinson's disease. The evidence on which this claim was made was the Attenuation of Disease Progression with Azilect Given Once Daily (ADAGIO) study (Olanow *et al* 2009).

Boehringer Ingelheim alleged that the invitation in effect promoted Azilect in a manner which was not in accordance with the terms of its marketing authorization; Azilect was not licensed to slow disease progression. Furthermore the ADAGIO study included a 2mg dose which was not licensed. The claim 'slowing disease progression' did not fairly represent the ADAGIO study and in that regard was misleading, could not be substantiated and did not encourage the rational use of Azilect. High standards had not been maintained and the special nature of medicines had not been recognised. Boehringer Ingelheim further alleged that the invitation had been distributed to the public who had thus been exposed to promotional messages for a prescription only medicine which might raise unfounded hopes of successful treatment.

The Panel noted that the symposium at issue consisted of three short presentations, 'The ADAGIO trial – key results, facts and misperceptions', 'Translating clinical study results into clinical practice and treatment guidelines' and 'The emerging algorithm for earlier (pre-motor) diagnosis of Parkinson's disease'. Although neither Azilect nor rasagiline were referred to on the invitation, some health professionals might nonetheless make the link between the ADAGIO study, the results of which had been published in September 2009, and Azilect. The ADAGIO study examined the possibility that Azilect had disease-modifying effects. Azilect was not licensed to slow Parkinson's disease progression.

The supplementary information to the Code stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion which was prohibited. The Panel did not know what was said at the symposium nor had it seen the ADAGIO study presentation; the complaint was only about the invitation.

The Panel did not consider that it was necessarily unacceptable to discuss the results of ADAGIO within a *bona fide* scientific symposium which met the supplementary information to the Code. There was no complaint before the Panel on this point. The Panel did not consider that it had been established that the invitation, as included in the health professionals' delegate bags, promoted Azilect to slow Parkinson's disease progression. No breach of the Code was ruled. The Panel considered that the statement 'Slowing disease progression in Parkinson's disease', as stated on the invitation, could be seen as aspirational and noted Lundbeck and Teva's submission that it was intended to reflect the whole meeting content. The Panel did not consider that the statement was misleading with regard to the outcome of the ADAGIO study or that it exaggerated the properties of Azilect and did not encourage rational use of the medicine. No breach of the Code was ruled.

The Panel noted that invitations had also been put in all of the delegate bags for patients/carers attending the congress. This should not have happened. The Panel did not consider, however, that the invitation was an advertisement for Azilect and in that regard it ruled no breach of the Code. Nonetheless the Panel considered that although patients/carers would not have been able to attend the symposium, the invitation was, in itself, enough for at least some of them to link Azilect with the slowing of disease progression in Parkinson's disease. In that regard the Panel considered that the invitation might encourage some patients to ask their prescribers to prescribe Azilect and that it also had the potential to raise unfounded hopes of successful treatment. A breach of the Code was ruled. The inclusion of the invitation in patients'/carers' delegate bags meant that high standards had not been maintained. A further breach of the Code was ruled.

The Panel did not consider that giving the invitation to patients/carers meant that the special nature of medicines had not been recognised. No breach of the Code was ruled. The Panel did not consider that the invitation was promotional material *per se* and in that regard no breach was ruled.

The Panel noted it's rulings of breaches of the Code above and considered that, *de facto*, not all applicable codes had been complied with. A breach of the Code was ruled.

The Panel noted that Boehringer Ingelheim had alleged a breach of that part of the Code which dealt with relationships with patient organisations. The Panel did not consider that the matter was covered by that part of the Code and thus ruled no breach.

Boehringer Ingelheim alleged that the presentation of results from the ADAGIO Study on an exhibition stand misrepresented the data and promoted Azilect for an unlicensed indication (ie to slow the clinical progression of Parkinson's disease). The claim Slowing clinical progression' was not substantiated by the ADAGIO data and did not encourage the rational use of Azilect. High standards had not been maintained.

The Panel noted that Azilect was licensed for the treatment of idiopathic Parkinson's disease as monotherapy, or with levodopa, at a dose of 1mg/day. Claims for Azilect on the exhibition stand referred to 'delayed clinical progression', 'slowing the clinical progression' and 'reduction in clinical progression'. Azilect was not authorized to slow clinical progression in Parkinson's disease. In that regard the Panel considered that the claims at issue were inconsistent with the particulars listed in the Azilect SPC and did not encourage the rational use of Azilect. Breaches of the Code were ruled.

The Panel noted that the claims for delayed disease progression were derived from the ADAGIO study. The ADAGIO study showed that early treatment with Azilect 1mg/day provided benefits that were consistent with a possible disease-modifying effect, but early treatment with Azilect 2mg/day did not. The authors concluded that given the negative findings for the 2mg dose, they could not definitely conclude that Azilect 1mg/day had disease modifying effects. The Panel thus considered that the claims at issue did not reflect the findings of the ADAGIO study and were misleading in that regard. The claims could not be substantiated by reference to the ADAGIO study. High standards had not been maintained. Breaches of the Code were ruled which were upheld on appeal.

Boehringer Ingelheim noted that visitors to the exhibition stand were encouraged, via a business card, to visit the website Mypdinfo.com which contained a guide to Parkinson's disease medicines. Boehringer Ingelheim noted that some medicines were mentioned but other, similar ones, were not. The section on medicines like Azilect stated that they were being investigated for slowing disease progression. The information provided was not a balanced view of UK therapies, it was not accurate or up-to-date and might raise unfounded hopes of successful treatment.

The Panel noted that a business card referring readers to the Mypdinfo website had been distributed from the Lundbeck/Teva exhibition stand. Neither the business card nor the website content had been approved for use in the UK; it appeared that it had been distributed by a non-UK company representative. Lundbeck and Teva acknowledged that they were responsible for the activities of other country affiliates and both companies had reinforced to global colleagues that activities taking place in the UK must conform with the UK Code.

The Panel noted that a document which could be downloaded from the website detailed dopamine agonists and although it was stated that ropinirole and rotigotine could be administered once daily it was not stated that pramipexole was also available in a once daily formulation. In that regard the Panel did not consider that the website gave a balanced, accurate and up-to-date overview of treatment options in the UK. A breach of the Code was ruled as alleged. The document also detailed MAO-B inhibitors and stated that rasagiline and seligiline were being investigated for their potential to slow disease progression. The Panel noted its comments above about the ADAGIO study and considered that the statement might encourage some members of the public to ask for either one of those specific medicines and raise unfounded hope of successful treatment. A breach of Code was ruled.

With regard to the section detailing future medicines, the Panel noted that the website contained the statement that 'recently published findings for the MAO-B inhibitor, rasagiline (Azilect), suggest that it could slow the progression of PD'. The Panel noted its comments above and considered that the statement did not accurately reflect the results of the ADAGIO study and was misleading in that regard. In the Panel's view, a statement that a medicine *could* produce a result, rarely negated the impression that it *would* produce that result. The Panel considered that the statement was unbalanced and would give patients/carers unfounded hope of successful treatment. Breaches of the Code were ruled.

Boehringer Ingelheim Limited complained about joint activities undertaken by Lundbeck Ltd and Teva Pharmaceuticals Ltd at the 2nd World Parkinson's Congress (WPC) in Glasgow, 22 September to 1 October 2010, to support Azilect (rasagiline), a medicine which they co-promoted for the treatment of Parkinson's disease. Boehringer Ingelheim stated that according to the congress organisers, patients comprised 20% of the approximately 3,600 delegates.

A Invitation to a pre-congress educational course entitled 'Slowing disease progression in Parkinson's disease'

The invitation (ref UK/AZI/1009/0030) was included in all delegate bags, including those of patients.

COMPLAINT

In Boehringer Ingelheim's view, 'Slowing disease progression in Parkinson's disease' implied that attendees would hear about a Parkinson's therapy that would slow progression of Parkinson's disease. The evidence on which this claim was made was the Attenuation of Disease Progression with Azilect Given Once Daily (ADAGIO) study (Olanow *et al* 2009).

The European Medicines Evaluation Agency (EMEA, now the European Medicines Agency, EMA) guideline on clinical investigation of medicines in Parkinson's disease required that to make a claim for disease modification, two criteria must be met: firstly, a demonstrated significant delay in clinical measures of disease progression; secondly, a quantifiable effect on the underlying pathophysiological process eg by biochemical markers or neuroimaging measures which correlated to a meaningful and persistent change in clinical function.

The ADAGIO study design did not address or meet the requirements of the EMEA guideline.

The ADAGIO study stated that early-start treatment with rasagiline 1mg/day met all end points in the primary analysis: a smaller mean (±SE) increase (which represented a worsening of the condition) in the unified Parkinson's disease rating scale (UPDRS) score between weeks 12 and 36 (0.09±0.02 points/week in the early-start group vs 0.14±0.01 points/week in the placebo group, p=0.01), a smaller increase in the score between baseline and week 72 (2.82±0.53 points in the early-start group vs 4.52±0.56 points in the delayed-start group, p=0.02), and non inferiority between the two groups with respect to the rate of change in the UPDRS score between weeks 48 and 72 (0.085±0.02 points/week in the early-start group vs 0.085±0.02 points/week in the delayed-start group, p<0.001). None of the three end points were met with rasagiline 2mg/day, since the change in the UPDRS score between baseline and week 72 was not significantly different in the two groups (3.47±0.50 points in the early start group and 3.11±0.50 points in the delayed-start group, p=0.60).

The authors concluded that early treatment with rasagiline 1mg/day provided benefits that were consistent with a possible disease-modifying effect, but early treatment with rasagiline 2mg/day did not. Because the two doses were associated with different outcomes, the authors stated that the study results must be interpreted with caution.

There was general consensus among experts that no medicine had adequately demonstrated neuroprotection or disease modification in Parkinson's disease patients.

The lack of widely accepted clinical or brain imaging criteria for disease-modification and the lack of diagnostic markers to monitor the effects of a treatment intervention in very early disease remained important hurdles to overcome.

Boehringer Ingelheim alleged that the nature of the invitation – the title of the session, the presentation titles and the fact that the invitation was inserted into all delegate bags including those of patients, breached the following clauses of the 2008 Code:

- 3.2 – promotion of a medicine in accordance with the terms of its marketing authorization, in that Azilect was not licenced to slow disease progression and was clearly the product discussed in the satellite symposium. Furthermore, the ADAGIO study, which was the topic of the first presentation, studied two doses, including a 2mg dose for which there was no marketing authorization.

- 7.2 – the claim was not accurate, balanced, fair or objective. It was misleading in the presentation of the ADAGIO study results, which did not meet its primary endpoint for both doses studied.

- 7.4 – the claim 'Slowing disease progression' could not be substantiated using the EMA criteria in the ADAGIO study design, or from Olanow *et al*.

- 7.10 – the claim of 'Slowing disease progression' did not encourage the rational use of Azilect by presenting it objectively and without exaggerating its properties.

- 9.1 – by exposing patients to the claim 'Slowing disease progression' in the invitation, high standards had not been maintained.

- 9.2 – exposing patients to the claim 'Slowing disease progression' did not recognise the special nature of medicines.

- 11.1 - the public were invited to a satellite symposium designed for health professionals and exposed to promotional messages for a prescription only medicine.

- 22.1 – the invitation advertised a prescription only medicine to the public. Azilect was the only product for Parkinson's disease jointly marketed by Teva and Lundbeck and the subject of the ADAGIO study, data from which was presented in the satellite symposium.

- 22.2 – the invitation did not present information to patients in a factual or balanced way. It might raise unfounded hopes of successful treatment with rasagiline.

Boehringer Ingelheim was concerned by the tone and content of inter-company correspondence on the matter as, in summary, Lundbeck and Teva considered that there was no breach of the Code because Azilect was not mentioned by name in the invitation and that they were not responsible for the distribution of the invitation in the delegate bags by the congress organisers.

Under Clause 1.3, the term medicine meant any branded or unbranded medicine intended for use in humans which required a marketing authorization. Avoidance of use of a brand name was not a defence; previous cases had demonstrated that companies were responsible for materials and activities where there was sufficient information provided to identify the product (eg Case AUTH/1873/8/06). Boehringer Ingelheim considered that in the invitation, use of the Lundbeck and Teva corporate logos and reference to the ADAGIO study was sufficient to identify that the product was Azilect.

Under Clause 1.1, UK pharmaceutical companies were responsible for activities undertaken by other country affiliates or corporate head offices in the UK, events at which UK clinicians were present and activities and events at which UK patients were present. Sponsorship of scientific meetings was specifically referred to in Clause 1.2.

Under Clauses 1.7, 20 and 23 of the 2008 Code, UK pharmaceutical companies were responsible for ensuring that patient organisations, consultants and third parties (agencies, congress organisers and the like) were aware of the Code and the responsibilities associated with compliance in connection with materials and activities conducted in the UK, or at events where UK clinicians and patients were present. Boehringer Ingelheim alleged that inclusion of the invitation in the delegate bag advertised a prescription only medicine to the patient/members of the public attendees, in breach of Clauses 22.1, 1.7, 20 and 23.

RESPONSE

Lundbeck and Teva submitted a joint response and stated that the invitation was for a scientific satellite symposium, organised and Continuing Medical Educational (CME) accredited by the congress and supported by an unrestricted educational grant from Teva and Lundbeck (as stated on the invitation) corporate departments. The invitation was designed by corporate colleagues and approved in the UK. The symposium was part of an educational day that preceded the main congress and, as such, was intended for health professionals only. This was confirmed on the congress website which stated:

> 'Pre-congress educational course #1
> Scientific Course Tuesday, September 28, 2010
>
> Note: as per UK pharmaceutical code, these sessions in Course #1 will be open only to healthcare professionals due to the nature of the talks and specific drug treatments that will be discussed. All courses have been designed by the WPC leadership.'

Patients attending the congress would be expected to arrive the following day. In supporting the meeting, Teva and Lundbeck expected that the congress organisers would distribute the invitation only to health professionals via the delegate bags. Lundbeck and Teva did not have control over the actual distribution of the invitation and it appeared they were also included in the patient delegate bags. This should not have happened and both companies had reviewed this incident and would ensure this issue was addressed for any future meetings. Due to the timing of the meeting it was, however, unlikely that any patients would have been at the conference during the meeting. Furthermore, health professionals and patients had different conference identity badges which were checked on entry to the meeting to ensure only health professionals were permitted access.

The invitation did not refer to Azilect nor did it contain any promotional claims for rasagiline. It was an invitation to a non-promotional educational meeting and outlined the presentation topics. The title of the meeting was intended to reflect the whole meeting content as a wide ranging discussion of 'Slowing disease progression in Parkinson's disease' as an important research and therapeutic goal in Parkinson's disease. This was in keeping with the educational nature and organisation of the meeting rather than focussing simply on the effects of medicines or indeed the promotion of rasagiline. In support of this, only the first of the three presentations featured a specific clinical study (a double-blind, delayed-start trial of rasagiline in Parkinson's disease (the ADAGIO study)) which was very reasonable given that this was recently published in the New England Journal of Medicine and evaluated one of the EMA's key parameters for a disease modifying effect (referred to by Boehringer Ingelheim), namely an effect on clinical disease progression. Such studies were notoriously difficult to conduct, were few in number and this one, which included rasagiline, was a high profile publication in the Parkinson's disease academic community which merited inclusion in any current discussion around the role of medicines on disease progression.

Lundbeck and Teva noted that they had sponsored this pre-congress educational course via an unrestricted educational grant in association with the congress as an educational meeting for health professionals and not as a promotional meeting for rasagiline. As this was not a promotional meeting for rasagiline and the invitation did not contain any promotional claims for the product; the companies did not accept the alleged breaches of Clauses 3.2, 7.2, 7.4, 7.10, 9.1, 9.2, 11.1, 22.1 and 22.2.

The companies did accept that, due to the unanticipated distribution process of the conference organisers, invitations had been put into patient delegate bags. As mentioned, the conference organisers were clear that only health professionals were to attend the symposium, and the event took place before patient activities commenced.

Teva and Lundbeck therefore did not accept that the invitation in question promoted rasagiline.

PANEL RULING

The Panel noted that the invitation at issue was to a satellite symposium held as part of a formal pre-congress educational course. The title of the symposium was 'Slowing disease progression in Parkinson's disease'. The symposium consisted of three short presentations, 'The ADAGIO trial – key results, facts and misperceptions', 'Translating clinical study results into clinical practice and treatment guidelines' and 'The emerging algorithm for earlier (pre-motor) diagnosis of Parkinson's disease'. The Panel accepted that although neither Azilect nor rasagiline were referred to on the invitation, some health professionals might nonetheless make the link between the ADAGIO study, the results of which had

been published in the New England Journal of Medicine in September 2009, and Azilect. The ADAGIO study examined the possibility that Azilect had disease-modifying effects. Azilect was not licensed to slow Parkinson's disease progression.

The Panel noted that the supplementary information to Clause 3, Marketing Authorization, stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion which was prohibited under Clause 3 or any other clause. The Panel did not know what was said at the symposium nor had it seen the ADAGIO study presentation; the complaint was only about the invitation.

The Panel did not consider that it was necessarily unacceptable to discuss the results of ADAGIO within a *bona fide* scientific symposium which met the supplementary information to Clause 3. There was no complaint before the Panel on this point. The Panel did not consider that it had been established that the invitation, as included in the health professionals' delegate bags, promoted Azilect to slow Parkinson's disease progression. No breach of Clause 3.2 was ruled. The Panel considered that the statement 'Slowing disease progression in Parkinson's disease', as stated on the invitation, could be seen as aspirational and noted Lundbeck and Teva's submission that it was intended to reflect the whole meeting content. The Panel did not consider that the statement was misleading with regard to the outcome of the ADAGIO study. No breach of Clause 7.2 was ruled. The Panel also ruled no breach of Clause 7.4. The Panel did not consider that the statement exaggerated the properties of Azilect and did not encourage rational use of the medicine. No breach of Clause 7.10 was ruled.

The Panel noted that invitations had also been put in all of the delegate bags for patients/carers attending the congress. This should not have happened. The Panel did not consider, however, that the invitation was an advertisement for Azilect and in that regard it ruled no breach of Clause 22.1. Nonetheless the Panel considered that although patients/carers would not have been able to attend the symposium, the invitation was, in itself, enough for at least some of them to link Azilect with the slowing of disease progression in Parkinson's disease. In that regard the Panel considered that the invitation might encourage some patients to ask their prescribers to prescribe Azilect and that it also had the potential to raise unfounded hopes of successful treatment. A breach of Clause 22.2 was ruled. The inclusion of the invitation in patients'/carers' delegate bags meant that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel did not consider that giving the invitation to patients/carers meant that the special nature of medicines had not been recognised. No breach of Clause 9.2 was ruled. The Panel did not consider that the invitation was promotional material *per se* and in that regard there could be no breach of Clause 11.1. The Panel ruled accordingly.

The Panel noted it's rulings of breaches of the Code above and considered that, *de facto*, not all applicable codes had been complied with. A breach of Clause 1.7 was ruled.

The Panel noted that Boehringer Ingelheim had alleged a breach of Clause 23. Clause 23 set out the requirements for the relationships between pharmaceutical companies and patient organisations. The Panel did not consider that the matter was covered by Clause 23 which dealt in the main with issues of transparency. Materials distributed to patients was covered by Clause 22. The Panel thus ruled no breach of Clause 23.

B The presentation of results from the ADAGIO study on an exhibition stand

COMPLAINT

Boehringer Ingelheim alleged that the exhibition stand used a moving visual image/slide show which misrepresented the ADAGIO data. Statements on the exhibition stand, referenced to Olanow *et al*, included:

'delivers the dual benefit of delayed clinical progression with improved symptomatic control in Parkinson's disease'

'the only treatment to demonstrate slowing the clinical progression and symptomatic efficacy in PD in a prospective delayed start study'

'provides patients with 38% reduction in clinical progression at 72 weeks'

Boehringer Ingelheim alleged that the claims were in breach of the following clauses of the 2008 Code:

- 3.2 – promotion of a medicine in accordance with the terms of its marketing authorization, in that Azilect was not licenced to slow clinical progression; the 2mg dose reported in the ADAGIO study, the results of which did not reach statistical significance, has no marketing authorization for the treatment of Parkinson's disease or for slowing disease progression.

- 7.2 – the claim 'Slowing clinical progression' was not accurate, balanced, fair or objective. It was misleading in the presentation of the ADAGIO study results, which did not meet its primary endpoint for both doses studied.

- 7.4 – the claim 'Slowing clinical progression' was not substantiated by Olanow *et al*.

- 7.10 – the claim 'Slowing clinical progression' did not encourage the rational use of Azilect by presenting it objectively and without exaggerating its properties.

- 9.1 – by presenting the ADAGIO data in this way, high standards had not been maintained.

Boehringer Ingelheim was concerned by the tone and content of inter-company correspondence on the matter as Lundbeck and Teva considered that because they did not actively promote 2mg rasagiline, the use of the ADAGIO study in promotional material and activities was acceptable.

Reference to the ADAGIO study on the exhibition stand, drew health professionals' attention to the study results, the study design and the inclusion of a 2mg rasagiline arm. In Case AUTH/2263/9/09 the Panel considered that, given the inclusion of an unlicensed dosing regimen in the ArTEN study, the advertisement at issue in effect constituted promotion that was inconsistent with the particulars listed in the summary of product characteristics (SPC) in breach of Clause 3.2. Boehringer Ingelheim alleged that the promotional messages based on ADAGIO results displayed on the exhibition stand constituted promotion that was inconsistent with the particulars listed in the Azilect SPC in breach of Clause 3.2.

The ADAGIO study results claimed 38% less clinical progression for the early start arm compared with the delayed start arm. The authors stated that the clinical significance of this difference, which reflected a difference of 1.7 UPDRS points between the early start and delayed start groups that received rasagiline 1mg/day was not known.

RESPONSE

Lundbeck and Teva noted that in Point A above, Boehringer Ingelheim had cited the EMA guideline on investigation of medicines for Parkinson's disease which stated that to demonstrate disease modification on Parkinson's disease a medicine must demonstrate a significant delay in clinical measures of disease progression and an effect on the underlying pathophysiology of the disease (eg biomarkers or neuroimaging measures). Boehringer Ingelheim appeared to have confused disease modification with slowing clinical progression. The EMA guidelines drew a clear distinction between them. All the companies' communications about ADAGIO were restricted to objective presentation of the demonstrated effect on clinical progression that was achieved by treating earlier with rasagiline vs delaying treatment for 36 weeks. In addition, they highlighted other symptomatic benefits of treatment with rasagiline, in accordance with the marketing authorization. Both these treatment approaches used 1mg rasagiline and clearly fell within the EU indication.

The companies had also included a personal testimony from a key opinion leader in Parkinson's disease who was additionally one of the main investigators in the ADAGIO study. This testimony further illustrated a clinician's perspective on the difference between agents which might influence disease modification and those which might affect clinical progression.

The ADAGIO study demonstrated a significant delay in clinical progression for rasagiline 1mg as the second part of its hierarchical Primary Endpoint (table 2; page 1274; -1.68 ± 0.75, p=0.02, also referred to was figure 3A, page 1275 for graphical representation). In essence, the group who started with 1mg rasagiline monotherapy (as per the current EU licence) at the beginning of the study had a significant delay to their clinical disease progression compared with those who started 1mg rasagiline monotherapy (as per the current EU licence) 36 weeks later. This result addressed the first criterion of the EMA guideline. Biomarkers or neuroimaging were not investigated in the ADAGIO study. None of the claims cited by Boehringer Ingelheim discussed disease modification. All claims only referred to the effects on clinical progression that were demonstrated by 'within licence' use of rasagiline 1mg in the ADAGIO study. These two were distinct and separate phenomena within the EMA guideline. Additionally, rasagiline 2mg was not a licensed dose anywhere in the world and was therefore not discussed in promotional materials.

Lundbeck and Teva noted that all patients who received 1mg rasagiline in the ADAGIO study were eligible for treatment according to the terms of the current Azilect marketing authorization. With respect to the current promotion of Azilect, the results from the 2mg rasagiline arm of the study could be considered irrelevant as this dose was not licensed anywhere in the world and all promotional use of the ADAGIO study referred only to data which were within the scope of the present marketing authorization.

It was not unusual for clinical studies to produce results that were difficult to interpret, particularly in relation to dose and clinical response. The ADAGIO authors proposed a number of explanations for the differing rasagiline 1mg and 2mg study arm results. This remained a well designed and conducted clinical study and the results for the 1mg rasagiline arm on clinical progression were scientifically robust and not invalidated by the fact that the 2mg rasagiline arm did not show a similar outcome.

With regard to Clause 3.2, Lundbeck and Teva noted that the Azilect marketing authorization included the indication for treatment of Parkinson's disease as monotherapy. ADAGIO assessed the impact on clinical progression of starting monotherapy immediately after diagnosis vs starting monotherapy 36 weeks later. This comparison of Parkinson's disease treatment strategy demonstrated a significant difference in symptom progression by 72 weeks as part of the study's primary outcome ie treating early was advantageous over delaying treatment. Both treatment approaches, and therefore this result, were in accordance with the terms of the marketing authorization.

With regard to Clauses 7.2, 7.4 and 7.10, Lundbeck and Teva noted, as detailed above, that ADAGIO demonstrated that rasagiline slowed clinical progression as part of its primary endpoint in a

delayed start study design. Substantiation was Table 2; page 1274; -1.68 ± 0.75, p=0.02. The absolute values for UPDRS deterioration by 72 weeks were given in the same table (4.5 delayed start vs 2.8 early start ie 38% reduction in this measure of clinical progression when rasagiline was started early). With regard to Clause 7.2, Lundbeck and Teva noted that rasagiline 2mg was not a licensed dose anywhere in the world and was therefore not discussed in promotional materials. With regard to Clause 7.10 the companies noted that the claim was objective and without exaggeration.

With regard to Clause 9.1, Lundbeck and Teva submitted that Boehringer Ingelheim appeared to have confused disease modification with slowing clinical progression. As previously discussed, the EMA guidelines drew a clear distinction between them. The companies restricted their communications about ADAGIO to objective presentation of the demonstrated effect on clinical progression that was achieved by treating earlier with rasagiline vs delaying treatment for 36 weeks. Both these treatment approaches which used 1mg rasagiline clearly fell within the EU indication. High standards had been maintained.

PANEL RULING

The Panel noted that Azilect was licensed for the treatment of idiopathic Parkinson's disease as monotherapy, or with levodopa, at a dose of 1mg/day. Claims for Azilect on the exhibition stand referred to 'delayed clinical progression', 'slowing the clinical progression' and 'reduction in clinical progression'. Azilect was not authorized to slow clinical progression in Parkinson's disease. In that regard the Panel considered that the claims at issue were inconsistent with the particulars listed in the Azilect SPC. A breach of Clause 3.2 was ruled. The Panel considered that the claims did not encourage the rational use of Azilect. A breach of Clause 7.10 was ruled.

The Panel noted that the claims for delayed disease progression were derived from the ADAGIO study. The ADAGIO study showed that early treatment with Azilect 1mg/day provided benefits that were consistent with a possible disease-modifying effect, but early treatment with Azilect 2mg/day did not. The authors concluded that given the negative findings for the 2mg dose, they could not definitely conclude that Azilect 1mg/day had disease modifying effects. The Panel thus considered that the claims at issue did not reflect the findings of the ADAGIO study and were misleading in that regard. A breach of Clause 7.2 was ruled. The claims could not be substantiated by reference to Olanow *et al* (the ADAGIO study). A breach of Clause 7.4 was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

All of the Panel's rulings in Point B were appealed.

APPEAL BY TEVA and LUNDBECK

Teva and Lundbeck noted that the Panel's ruling concluded that Azilect was not authorized to slow clinical progression in Parkinson's disease. In that regard the Panel considered that the claims at issue were inconsistent with the particulars listed in the Azilect SPC. The claims at issue in the ruling were: '… delivers dual benefit of **delayed clinical progression** with improved symptomatic control in Parkinson's disease', '… the only treatment to demonstrate **slowing the clinical progression** and symptomatic efficacy in PD in a prospective delayed study' and '… provides patients with 38% **reduction in clinical progression** at 72 weeks' (emphasis added).

Parkinson's disease was a progressive neurodegenerative disease whose initial clinical features resulted from the loss of dopaminergic neurons in the substantia nigra pars compacta of the midbrain. The definition of Parkinson's disease was rather difficult. Diagnosing Parkinson's disease first required identifying parkinsonism (a syndrome characterised by rigidity, tremor and bradykinesia), loss of pigmented dopaminergic neurons in the brain stem (particularly in the pars compacta region of the substantia nigra) and the presence of neuronal intracytoplasmic inclusions called Lewy bodies.

There were currently no validated biomarkers established for Parkinson's disease. In theory, therefore, definitive diagnosis of Parkinson's disease required a post-mortem neuropathological examination. However, patient history and examination by skilled clinicians could establish the diagnosis with fairly high certainty; even today, the diagnosis of Parkinson's disease was based on clinical features and progress was monitored by clinical tools (the UPDRS being the most established). The UPDRS measured symptom burden at a point in time but when used serially over time it provided a measure of disease progression.

The slides used in the exhibition stand used the words 'clinical progression' rather than 'disease modification'. The key opinion leader's personal testimony set out definitions of 'clinical progression' and 'disease modification'. As he explained, the terms 'affecting clinical progression', 'slowing clinical progression' and 'delaying clinical progression' all implied a change in the clinical manifestations (symptoms and/or signs) of the syndrome but did not necessarily imply any change in the underlying disease process and, in fact, it was not possible to establish conclusively disease modifying effect of any intervention given the current understanding of Parkinson's disease, not least due to the lack of validated biomarkers and neuroimaging techniques.

The companies submitted that the EMA guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease clearly distinguished between disease progression and disease modification: 'If a delay in disease progression is shown, this does not imply that a new agent is also a disease modifier'. The above definition of disease

progression did not imply disease modification, ie changing the course of the underlying disease process. However, as these two terms sounded very similar they could lead to confusion among health professionals (even more so among those who were more engaged in the clinic and less in academia). Therefore, to avoid such confusion and present matters with more clarity, the companies had used 'clinical progression' instead of 'disease progression' in their materials to accurately reflect the simple observation of clinical UPDRS over time without any implication as to an effect on the underlying pathology.

Azilect was indicated for the treatment of idiopathic Parkinson's disease as monotherapy (without levodopa) or as adjunct therapy (with levodopa) in patients with end of dose fluctuations. Some of the data referenced in Azilect's SPC (specifically study 1 in Section 5.1) examined the efficacy of Azilect by reference to statistically significant differences in UPDRS scores. Such data, self-evidently, supported Azilect's licensed therapeutic indication for the monotherapy of idiopathic Parkinson's disease. The slowing of clinical progression claims at issue here were also evidenced by a statistically significant difference in UPDRS scores (discussed in more detail below), showing the consistency of such claims with the SPC.

Based on the SPC (monotherapy for the treatment of Parkinson's disease), treatment goals in Parkinson's disease (symptom control) and the previously discussed meaning of 'clinical progression' (worsening of symptoms), the companies submitted that the claims 'slowing clinical progression', 'delayed clinical progression' and 'reduction in clinical progression' were not inconsistent with the SPC. On these grounds, the companies did not accept that the ruling of a breach of Clause 3.2 was justified.

Furthermore, on the basis of the above in relation to the consistency of the claims at issue with the SPC, the companies disagreed that the claims did not encourage the rational use of Azilect. The companies therefore denied a breach of Clause 7.10.

In its ruling about the ADAGIO study the Panel 'noted that the claims for **delayed disease progression** were derived from the ADAGIO study. The ADAGIO study showed that early treatment with Azilect 1mg/day provided benefits that were consistent with a possible **disease-modifying effect**, but early treatment with Azilect 2mg/day did not. The authors concluded that given the negative findings for the 2mg dose, they could not definitely conclude that Azilect 1mg/day had **disease modifying effects**. The Panel thus considered that the claims at issue did not reflect the findings of the ADAGIO study and were misleading in that regard' (emphasis added). The claims at issue were those referred to above.

The companies noted the reference in the first sentence above to 'claims for delayed disease progression'. The claims at issue all referred to clinical progression, not disease progression. The term 'clinical progression', was used with intention to clarify that the symptomatic effect was present not just at a single time point, but lasted for the duration of the study, thereby producing a statistically significant reduction/delay/slowing in clinical progression. The ADAGIO study was designed to examine the possibility that Azilect had a disease modifying effect in Parkinson's disease. It produced robust and very useful data and demonstrated the clinical benefit of early treatment with Azilect. The ADAGIO study demonstrated a statistically significant delay in clinical progression for Azilect 1mg as the second part of its hierarchical primary endpoint (p=0.02). In essence, the group who started with Azilect 1mg monotherapy (as per the current EU licence) at the beginning of the study had a statistically significant delay to their clinical disease progression compared with those who started Azilect 1mg monotherapy (as per the current EU licence) 36 weeks later. These statistically significant data formed the basis of the claim that Azilect delayed clinical progression of Parkinson's disease. All claims only referred to the effects on clinical progression that were demonstrated by the licenced use of Azilect 1mg in the ADAGIO study.

Whilst Olanow *et al* stated that they 'cannot definitely conclude that rasagiline at a dose of 1mg per day has disease-modifying effects', this statement was an overall conclusion as to the hypothesis that rasagiline 1mg per day had disease-modifying effects. This statement did not, however, mean that it could not be said that rasagiline 1mg per day delayed clinical progression of Parkinson's disease on the basis of statistically significant data from the ADAGIO study.

On this basis, the companies disagreed with the Panel's ruling that the claims were misleading and in breach of Clause 7.2. Furthermore, it was clear that the claims could be substantiated by Olanow *et al* and therefore did not breach Clause 7.4.

The companies noted that in relation to its rulings above, the Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1. The companies submitted that in considering whether or not high standards had been maintained, attention must be paid to the supplementary information to Clause 9.1, which listed a number of examples of situations where high standards had not been maintained eg the provision of private prescription forms pre-printed with the name of a medicine. The above set out in detail why the companies submitted that the claims at issue did not breach the Code. Whatever the Appeal Board's ruling, it was clear from the supplementary information to Clause 9.1 and previous Panel rulings on this clause that the claims made at an exhibition stand at the 2nd World Parkinson's Congress, were simply not the sort of claims in relation to which a ruling of a Clause 9.1 breach should be ruled. It was unreasonable and incorrect to place them in the same category as the promotional materials referred to in the supplementary information to Clause 9.1. The companies submitted that high standards were, by some margin, maintained throughout and thus denied a breach of Clause 9.1.

COMMENTS FROM BOEHRINGER INGELHEIM

Boehringer Ingelheim had no further comments.

APPEAL BOARD RULING

The Appeal Board noted that the authors of the ADAGIO study stated that their study results must be interpreted with caution. Although the study showed that early treatment with Azilect 1mg/day provided benefits consistent with a possible disease-modifying effect, early treatment with Azilect 2mg/day did not. The authors concluded that given the negative findings for the 2mg dose, they could not definitely conclude that Azilect 1mg/day had disease modifying effects.

The Appeal Board did not accept the companies' submission that the phrase 'clinical progression' in the video looped screen shots related to symptoms not 'disease modification'. All three screen shots were referenced to the ADAGIO study. The Appeal Board noted that the first screen shot stated 'Delivers the dual benefit of delayed clinical progression with improved symptomatic control in Parkinson's disease'. The Appeal Board considered that the implication was that the 'dual benefit' was 'delayed clinical progression' *and* 'improved symptomatic control'.

Similarly the second screen shot referred to 'slowing the clinical progression' and 'symptomatic efficacy'. The Appeal Board considered that by distinguishing between clinical progression and symptom control the material implied that clinical progression was in effect 'disease modification'. The Appeal Board considered that this implication was compounded by the third screen shot at issue which featured a bar chart that compared the mean UPDRS change from baseline for Azilect delayed-start vs Azilect early-start. The bar chart included the statement 'Data presented for the licensed dose only'. A statistically significant advantage for Azilect early-start was shown (p=0.02). At the top of the screen shot was the claim 'Provides patients with 38% reduction in clinical progression' at 72 weeks. However, the screen failed to convey the authors' conclusions that, given the negative findings for the 2mg dose, they could not definitely conclude that Azilect 1mg/day had disease modifying effects.

The Appeal Board noted that Azilect 1mg/day was licensed for the treatment of idiopathic Parkinson's disease as monotherapy, or with levodopa. Azilect was not authorized to slow clinical progression in Parkinson's disease. The Appeal Board considered that the claims at issue were inconsistent with the particulars listed in the Azilect SPC. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The Appeal Board considered that the claims did not encourage the rational use of Azilect. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.10. The appeal on both points was unsuccessful.

In addition, the Appeal Board considered that the claims at issue did not reflect the findings of the ADAGIO study and were misleading in that regard as alleged. The claims could not be substantiated by Olanow *et al* (the ADAGIO study). The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

The Appeal Board noted its rulings above and considered that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

C Link to Mypdinfo.com

COMPLAINT

Boehringer Ingelheim stated that visitors to the exhibition stand in the public area of the exhibition hall, including patients, were encouraged to follow a link to the website www.Mypdinfo.com, provided through a business card. The website contained a guide to Parkinson's disease medicines, available for download as a PDF. Under the section on dopamine agonists, once daily formulations of rotigotine and ropinirole were mentioned, but not pramipexole (Boehringer Ingelheim's product Mirapexin Prolonged Release, launched in the UK in October 2009). The section on monoamine oxidase-B (MAO-B) inhibitors [such as Azilect] stated that they were being investigated for slowing disease progression, but the same was not discussed for the dopamine agonists or pramipexole. This did not provide a balanced view of current available therapies for UK patients. Boehringer Ingelheim alleged breaches of Clause 7.2, in that the information was not accurate or up-to-date and Clause 22.2 in that the information presented might raise unfounded hopes of successful treatment.

Specifically, within the website section on future medicines the following information was given about slowing disease progression (last accessed by Boehringer Ingelheim 26 October 2010):

> 'One of the key research targets for Parkinson's disease (PD) is finding a way to stop the disorder developing and progressing – ie, finding a treatment to modify the disease course. However, this effect is difficult to measure in a clinical study, and it also requires many years of follow-up to confirm any outcomes.
>
> Despite these problems, several PD medications have been investigated in trials specifically designed to assess the rate of disease progression, and recently published findings for the MAO-B inhibitor, rasagiline (Azilect), suggest that it could slow the progression of PD. The dopamine agonist, pramipexole (Mirapexin), is also being investigated for this purpose, although study results are not yet available.
>
> Currently, no medication is approved/licensed for modifying PD progression, although this possibility remains an exciting prospect for the future.'

This statement did not reflect the current state of clinical research in regard to the publication of study results. Boehringer Ingelheim alleged breaches of Clauses 7.2 and 22.2.

Boehringer Ingelheim was concerned by the tone and content of inter-company correspondence on the matter as, in summary, Lundbeck and Teva considered that because the Mypdinfo.com was a European patient information site, with no links to UK affiliates of either company, they were not responsible.

The business card referring to the website was available from the Teva/Lundbeck exhibition stand in the public area of the exhibition hall, accessible to health professionals, patients and members of the public, including those from the UK. As Teva and Lundbeck were responsible under the Code for activities at this congress, Boehringer Ingelheim refuted their assertion that they did not direct UK health professionals or patients to the website.

RESPONSE

Lundbeck and Teva noted that Mypdinfo.com was a European patient information site with the content authored and provided by the European Parkinson's Disease Association (EPDA). The companies supported the website on a Europe-wide basis through non-UK company departments. Neither UK affiliate had any direct association with the support of this website and neither directed UK patients or health professionals to it. The companies did not dispute the existence of the business card with the website address and having reviewed those attending the meeting representing both companies and the related activities they concluded that the card in question was distributed by a non-UK company representative at the exhibition stand.

With regard to the quoted content from the website, it stated clearly that no medicines were currently approved/licensed for slowing disease progression in Parkinson's disease, although this possibility remained an exciting prospect for the future. The companies believed this was an accurate reflection of research in this area and consequently would not raise unfounded hopes of successful treatment amongst the public. They accepted that they were responsible for all activities undertaken by other country affiliates or corporate head offices in the UK. As such, all material distributed at the stand should have been approved under the Code. This did not happen with regard to the Mypdinfo.com business card and the actual site content. Both companies had therefore, as a matter of priority, reinforced to global company colleagues that all activities relating to international scientific meetings taking place in the UK must conform to the requirements of the Code.

PANEL RULING

The Panel noted that a business card referring readers to the Mypdinfo website had been distributed from the Lundbeck/Teva exhibition stand. Neither the business card nor the website content had been approved for use in the UK; it appeared that it had been distributed by a non-UK company representative. The Panel noted Lundbeck and Teva's acknowledgement that they were responsible for the activities of other country affiliates and that both companies had reinforced to global colleagues that activities taking place in the UK must conform with the UK Code. Lundbeck and Teva had not commented on the website content.

The Panel noted that a PDF document which could be downloaded from the website detailed dopamine agonists and although it was stated that ropinirole (ReQuip and ReQuip LP) and rotigotine (Neupro) could be administered once daily it was not stated that pramipexole (Mirapexin) was also available in a once daily formulation. In that regard the Panel did not consider that the website gave a balanced, accurate and up-to-date overview of treatment options in the UK. A breach of Clauses 7.2 was ruled as alleged. The PDF document also detailed MAO-B inhibitors and stated that rasagiline (Azilect) and seligiline (Eldepryl) were being investigated for their potential to slow disease progression. The Panel noted its comments above about the ADAGIO study and considered that the statement might encourage some members of the public to ask for either one of those specific medicines and raise unfounded hope of successful treatment. A breach of Clause 22.2 was ruled.

With regard to the section detailing future medicines, the Panel noted that the website contained the statement that 'recently published findings for the MAO-B inhibitor, rasagiline (Azilect), suggest that it could slow the progression of PD'. The Panel noted its comments at B above with regard to the ADAGIO study. The Panel considered that the statement did not accurately reflect the results of that study and was misleading in that regard. In the Panel's view, a statement that a medicine *could* produce a result, rarely negated the impression that it *would* produce that result. A breach of Clause 7.2 was ruled. The Panel considered that the statement was unbalanced and would give patients/carers unfounded hope of successful treatment. A breach of Clause 22.2 was ruled.

Complaint received	**17 March 2011**
Case completed	**12 July 2011**

HOSPITAL CONSULTANT v WARNER CHILCOTT

Promotion of Asacol

A consultant physician and gastroenterologist complained about a leavepiece for Asacol (modified release (MR) mesalazine) issued by Warner Chilcott headed 'For moderately active ulcerative colitis (UC): Back to normal everyday life, sooner – Asacol 4.8g/day vs mesalazine 2.4g/day'. The leavepiece had been used with gastroenterologists and related health professionals. On opening the front flap, the right hand page featured the claim at issue, 'At 6 weeks, up to 72% of patients achieved treatment success (complete remission or clinical response to therapy) regardless of disease location'. Cited in support of the claim were three clinical trials assessing the safety and clinical efficacy of a new dose (ASCEND) of mesalazine (ASCEND I, II and III) (Hanauer *et al* 2007; Hanauer *et al* 2005; Sandborn *et al* 2009). Warner Chilcott submitted that these studies constituted the phase three clinical programme.

The complainant stated that the claim implied that using Asacol 800mg MR tablets, there would be a treatment success of 72%, either with complete remission or clinical response. The complainant alleged that this was misleading as the ASCEND studies reported remission rates of less than 20%.

The detailed response from Warner Chilcott is given below.

The Panel noted that treatment success was defined in the three ASCEND studies as either a complete response (remission) or a clinical or partial response (improvement) to treatment from baseline at week 6. In ASCEND I, 72% of patients with moderate disease treated with Asacol 4.8g/day, achieved overall improvement. It was not reported how many of these patients had a complete response to therapy. In ASCEND II, 71.8% of patients with moderate disease treated with Asacol 4.8g/day were classified as having overall improvement; 20.2% achieved complete remission and 51.6% had a clinical response to therapy. At week 6 in the ASCEND III study 70.2% 273/389 of patients receiving Asacol 4.8g/day achieved treatment success; complete and partial response rates were 2.6% and 67.6% respectively.

The Panel noted that the implication of the ASCEND data was that in approximately 30% of patients, treatment with Asacol 4.8g/day resulted in neither remission nor improvement, as defined by the studies.

The Panel noted that the front cover of the leavepiece referred to 'Back to normal everyday life, sooner'. The claim at issue was 'At 6 weeks, up to 72% of patients achieved treatment success (complete remission or clinical response to therapy) regardless of disease location'. In the Panel's view most readers would assume that 'treatment success' meant a complete response to therapy ie remission. This was not so. The Panel did not consider that the qualification '(complete remission or clinical response to therapy)' was sufficiently detailed such as to allow readers to understand the significance of the data. Results from the ASCEND studies suggested that prescribers were more likely to see patients with a partial response, or neither remission nor improvement as defined in the studies, to Asacol 4.8g/day therapy than those in remission. The Panel considered that the claim was misleading and exaggerated; the data did not substantiate the impression given by the claim. Breaches of the Code were ruled.

Upon appeal by Warner Chilcott the Appeal Board noted that the ASCEND studies were conducted to support the registration of Asacol 800mg MR tablets. The primary endpoint in the study programme was the proportion of patients who achieved 'treatment success' at week 6. 'Treatment success' was a composite endpoint defined in ASCEND I and II as either complete remission or clinical response to therapy. In ASCEND III it was defined as either a complete response (remission) or a partial response (improvement) to treatment. The Appeal Board noted that the reference to treatment success in the claim 'At 6 weeks, up to 72% of patients achieved treatment success (complete remission or clinical response to therapy) regardless of disease location' was immediately followed by the definition '(complete remission or clinical response to therapy)'.

The Appeal Board noted that the ASCEND studies used the terms 'treatment success' and 'overall improvement' interchangeably. The Appeal Board noted that the leavepiece was intended for use with gastroenterologists and related health professionals. In the Appeal Board's view the term 'treatment success' in the context of ulcerative colitis, although defined and derived from the ASCEND studies, would, nonetheless, be understood by the specialists to whom the leavepiece was aimed. The claim included a definition of 'treatment success'.

The Appeal Board did not consider that the claim at issue was misleading or exaggerated as alleged and ruled no breaches of the Code. The Appeal Board considered that the claim did not imply that 72% of patients treated with Asacol 4.8g/day would achieve complete remission; rather that 72% of patients would achieve either a partial or complete response to therapy. The claim therefore could be

substantiated by the ASCEND studies. No breach of the Code was ruled. The appeal on all points was successful.

A consultant physician and gastroenterologist complained about a six page, gate-fold leavepiece for Asacol (modified release (MR) mesalazine) (ref AS8538) issued by Warner Chilcott. The leavepiece was headed 'For moderately active ulcerative colitis (UC): Back to normal everyday life, sooner – Asacol 4.8g/day vs mesalazine 2.4g/day'. On opening the front flap, the right hand page featured the claim 'At 6 weeks, up to 72% of patients achieved treatment success (complete remission or clinical response to therapy) regardless of disease location'. Cited in support of the claim were three clinical trials assessing the safety and clinical efficacy of a new dose (ASCEND) of mesalazine (ASCEND I, II and III) (Hanauer *et al* 2007; Hanauer *et al* 2005; Sandborn *et al* 2009). Warner Chilcott submitted that these studies constituted the phase three clinical programme.

Warner Chilcott representatives had used the leavepiece with gastroenterologists and related health professionals, such as irritable bowel disease nurses, with an interest in gastroenterology and ulcerative colitis.

COMPLAINT

The complainant stated that within the leavepiece, there was an implication that using Asacol 800mg MR tablets, there would be a treatment success of 72%, either with complete remission or clinical response. The complainant alleged that this was misleading as the actual remission rates reported in the ASCEND studies I, II and III, were less than 20%.

The Authority asked Warner Chilcott to respond in relation to Clauses 7.2, 7.4 and 7.10 of the Code.

RESPONSE

Warner Chilcott stated that within the ASCEND programme the primary endpoint was the proportion of patients in each treatment group which achieved treatment success at six weeks. Overall improvement was a term synonymous with treatment success, as described in the clinical papers. Treatment success was defined as either complete remission or clinical response to therapy, as detailed in ASCEND I, II and III (Hanauer *et al* 2007 and 2005 and Sandborn *et al*).

For patients with moderately active ulcerative colitis receiving Asacol 4.8g/day, dosed with the 800mg MR, 72% (55/76), 71.8% (89/124) and 70.2% (273/389) of patients achieved treatment success at week 6, in ASCEND I, II and III, respectively.

Warner Chilcott submitted that the claim reflected the findings presented in the ASCEND papers and as such it considered the claim was accurate, fair and balanced and consistent with Clause 7.2. The claim was substantiable; citation and reference details were included in the leavepiece. Warner Chilcott thus considered the claim was consistent with Clause 7.4. Treatment success was demonstrated across all three studies in the proportion presented in the claim and had not been exaggerated. As such, Warner Chilcott considered this to only encourage rational use of the medicine, thus upholding Clause 7.10.

In response to a request for further information, Warner Chilcott provided copies of a poster and of an abstract by Sandborn *et al* (2006).

PANEL RULING

The Panel noted that treatment success was defined in the three ASCEND studies as either a complete response (remission) or a clinical or partial response (improvement) to treatment from baseline at week 6. Each study defined the parameters used to assess the clinical response or partial response.

The ASCEND I trial studied patients with mild to moderate active ulcerative colitis. In patients with moderate disease treated with Asacol 4.8g/day, 72% (55/76) achieved overall improvement. It was not reported how many of these patients had a complete response to therapy.

ASCEND II only included those with moderate disease and of those treated with Asacol 4.8g/day, 71.8% (89/124) were classified as having overall improvement; 25 patients (20.2%) achieved complete remission and 64 patients (51.6%) had a clinical response to therapy.

The ASCEND III trial also only included patients with moderate ulcerative colitis. At week six, 70.2% (273/389) of patients receiving Asacol 4.8g/day achieved treatment success; complete and partial response rates were 2.6% and 67.6% respectively.

The Panel noted that the implication of the ASCEND data was that in approximately 30% of patients, treatment with Asacol 4.8g/day resulted in neither remission nor improvement, as defined by the studies.

The Panel noted that the front cover of the leavepiece referred to 'Back to normal everyday life, sooner'. The claim at issue was 'At 6 weeks, up to 72% of patients achieved treatment success (complete remission or clinical response to therapy) regardless of disease location'. In the Panel's view most readers would assume that 'treatment success' meant a complete response to therapy ie remission. This was not so. The Panel did not consider that the qualification '(complete remission or clinical response to therapy)' was sufficiently detailed such as to allow readers to understand the significance of the data. Results from the ASCEND studies suggested that prescribers were more likely to see patients with a partial response, or neither remission nor improvement as defined in the studies, to Asacol 4.8g/day therapy than those in remission. The Panel considered that the claim was

misleading and exaggerated. Breaches of Clauses 7.2 and 7.10 were ruled. The Panel did not consider that the data was such as to substantiate the impression given by the claim. A breach of Clause 7.4 was ruled.

APPEAL BY WARNER CHILCOTT

Warner Chilcott considered that the claim at issue was fully substantiated by reference to an approved, clinically meaningful endpoint of the pivotal clinical studies that supported Asacol. Furthermore, it was not misleading or exaggerated, as the claim did not refer only to complete remission rates, nor did the claim imply that 72% of patients achieved complete remission. Warner Chilcott thus denied breaches of Clauses 7.2, 7.4 and 7.10.

Warner Chilcott explained that the claim at issue was developed from the three ASCEND studies, which constituted the pivotal, phase three, clinical trial programme for Asacol 800mg MR tablets; the studies had been published in peer reviewed journals (Hanauer *et al* 2007 and 2005 and Sandborn *et al*).

Within the ASCEND clinical programme the primary endpoint was the proportion of patients in each treatment group that achieved treatment success at six weeks. This endpoint, which denoted clinical improvement, was clinically relevant and had been accepted by the Medicines and Healthcare products Regulatory Agency (MHRA)/Food and Drug Administration (FDA) when they granted Asacol 800mg MR tablets a marketing authorization. Treatment success, as described in the clinical papers and trial protocol, constituted 'complete remission or clinical response' to therapy. Treatment success was used synonymously with the term overall improvement in the ASCEND studies.

The ASCEND programme demonstrated the efficacy of Asacol 800mg MR tablets (4.8g/day) in patients with moderately active ulcerative colitis; 72% (55/76), 71.8% (89/124) and 70.2% (273/389) patients achieved the primary endpoint of treatment success (complete remission or clinical response to therapy) at week 6, in ASCEND I, II and III, respectively. These results fully reflected the details within the claim and therefore it was not in breach of Clause 7.2, 7.4 or 7.10.

Warner Chilcott submitted that the claim was in line with the studies and the Code; it had ensured that the meaning of treatment success was clear with the addition of a definition, as per the studies. Thus, in the leavepiece, 'treatment success' was immediately qualified by '(complete remission or clinical response to therapy)'.

The term 'treatment success' comprised patients who achieved either complete remission or a clinical response to therapy, as defined by the study protocol, and was accepted by the MHRA and FDA as a meaningful endpoint and measure to demonstrate the efficacy of Asacol 800mg MR tablets for moderately active ulcerative colitis. Thus patients in the ASCEND study programme had a positive, meaningful, successful treatment outcome ('treatment success') if they achieved complete remission of moderately active ulcerative colitis or demonstrated a clinical response to therapy, at six weeks of treatment:

- Complete remission: a complete resolution of ulcerative colitis signs and symptoms. Patients who achieved complete remission met the primary endpoint of treatment success.

- Clinical response to therapy: a positive change in signs and symptoms. In the ASCEND programme this constituted an improvement in some of the key clinical measures to assess activity of symptoms and severity of ulcerative colitis flare, from baseline at six weeks. 'Clinical response' was a well recognised and established term and did not mean 'remission'. Patients who achieved a clinical response to therapy met the primary endpoint of treatment success.

Therefore, in the ASCEND study programme up to 72% patients were considered as having treatment success, at six weeks, if they had achieved either complete remission or had demonstrated a clinical response to therapy.

In the claim, 'clinical response to therapy' was presented equally as one of two key parameters which comprised the overall treatment success measure used in the programme. The other component of which was remission. Thus it was clear that overall 'up to 72% patients achieving treatment success' comprised patients with either complete remission or clinical response to therapy. Therefore it was not reasonable to suggest that the claim implied 'remission', because 'clinical response to therapy' was equally presented within the claim, and thus was consistent with Clauses 7.2, 7.4 and 7.10.

Warner Chilcott noted that the Panel had referred to the front cover of the leavepiece and the claim 'Back to normal everyday life, sooner', which it linked to the claim at issue, and the assumption was made that 'most readers would assume that 'treatment success' meant a 'complete response'. In Case AUTH/2267/9/09 it was determined that the claim 'Back to normal everyday life, sooner', was not in breach of the Code, where the Panel stated that the implication was not that Asacol would return patients to a pre-ulcerative colitis state but was used to describe a patient returning to 'everyday activities'. The Panel also stated that it 'did not consider that 'normal' would be read as describing the patient's disease state'. In line with this ruling, Warner Chilcott considered that the impression created by the leavepiece now at issue was not that all patients would have a 'complete response to therapy, ie remission'.

Warner Chilcott submitted that the complainant appeared to have assumed that 'complete remission or clinical response to therapy' equated to 'remission'. If the claim had stated solely 'treatment success' without the qualifiers providing further definition, Warner Chilcott agreed that this could have misled the reader. Similarly, if the claim had stated 'treatment success (remission)' then this would have been incorrect and in breach of the Code.

Clinical response to therapy, a recognised and established term with health professionals, was sufficiently descriptive and did not require further explanation; it did not imply or mean complete remission. Warner Chilcott never made a claim for 'complete response'; this was an assumptive term introduced by the Panel.

When treatment success was stated in the leavepiece it was immediately followed and qualified by '(complete remission or clinical response to therapy)'. Warner Chilcott did not state or imply that treatment success would refer to, or only mean, those patients who achieved complete remission, and was therefore not in breach of the Code.

As stated by the Panel, 'Results from the ASCEND programme suggested that prescribers were more likely to see patients with a partial response, or neither remission nor improvement as defined in the studies, to Asacol 4.8g/day therapy than those in remission'. Indeed it was true that, based on the findings of the ASCEND studies, a physician was more likely to see patients with a partial response, ie a clinical response to therapy, and it was those very patients that were represented within the claim: '(complete remission or clinical response to therapy)'. Both the Panel and Warner Chilcott acknowledgement of the data, as noted above, concurred and the claim was neither misleading nor exaggerated and thus not in breach.

In summary, Warner Chilcott disagreed that the claim implied remission. As correctly stated by the Panel, 72% of patients with treatment success denoted those patients with either complete remission or clinical response to therapy; as was represented in the claim. The claim was technically correct, as substantiated by the approved and clinically relevant primary findings of the ASCEND clinical programme. As the claim was fully substantiated, Warner Chilcott denied a breach of Clause 7.4.

Warner Chilcott maintained that the claim was substantiated, was not exaggerated and provided the reader with enough information to make an informed prescribing decision; it was therefore not in breach of Clauses 7.2 and 7.10.

COMMENTS FROM THE COMPLAINANT

The complainant maintained that the claims could not be substantiated.

APPEAL BOARD RULING

The Appeal Board noted that the ASCEND studies were conducted to support the registration of Asacol 800mg MR tablets. The primary endpoint in the ASCEND study programme was the proportion of patients who achieved 'treatment success' at week 6. 'Treatment success' was a composite endpoint defined in ASCEND I and II as either complete remission or clinical response to therapy. ASCEND III defined treatment success as either a complete response (remission) or a partial response (improvement) to treatment. The Appeal Board noted that the reference to treatment success in the claim 'At 6 weeks, up to 72% of patients achieved treatment success (complete remission or clinical response to therapy) regardless of disease location' was immediately followed by the definition '(complete remission or clinical response to therapy)'.

The Appeal Board noted that all three ASCEND studies used the terms 'treatment success' and 'overall improvement' interchangeably. The Appeal Board noted that the leavepiece was intended for use with gastroenterologists and related health professionals, such as irritable bowel disease nurses with an interest in gastroenterology and ulcerative colitis. In that regard the Appeal Board noted that the leavepiece included advice on writing Asacol referral letters. In the Appeal Board's view the term 'treatment success' in the context of ulcerative colitis, although defined and derived from the ASCEND studies, would, nonetheless, be understood by the specialists to whom the leavepiece was aimed. The claim included a definition of 'treatment success'.

The Appeal Board did not consider that the claim at issue was misleading or exaggerated as alleged and ruled no breach of Clauses 7.2 and 7.10. The Appeal Board considered that the claim did not imply that 72% of patients treated with Asacol 4.8g/day would achieve complete remission; rather that 72% of patients would achieve either a partial or complete response to therapy. The claim therefore could be substantiated by the ASCEND studies. No breach of Clause 7.4 was ruled. The appeal on all points was successful.

Complaint received **6 April 2011**

Case completed **22 June 2011**

DIRECTOR/SHIRE v NORGINE

Promotion of Movicol

Shire complained about an advertisement and a leavepiece for Movicol Paediatric Plain (polyethylene glycol (macrogol) 3350 plus electrolytes) issued by Norgine. That part of the complaint which involved an alleged breach of undertaking was taken up by the Director as the Authority was responsible for ensuring compliance with undertakings.

Shire noted the prominent 'stamp' image on the advertisement which stated 'NICE [National Institute for health and Clinical Excellence] recommends MOVICOL Paediatric Plain FIRST-LINE' and submitted that Norgine had used this endorsement without the written permission of NICE.

The detailed responses from Norgine are given below.

The Panel did not consider that a statement that NICE had recommended a particular treatment meant that an official document had been reproduced as meant by the Code. No breach of the Code was ruled.

Shire noted that no reference was given to the NICE guidance referred to in the advertisement. The document referred to was CG99 'Constipation in children and young people: Diagnosis and management of idiopathic childhood constipation in primary and secondary care'.

The Panel noted that the Code required a reference to be given when promotional material referred to published studies. The claim at issue was not from a published study and it did not refer to a published study. No breaches of the Code were ruled.

Shire noted the stamp 'NICE recommends MOVICOL Paediatric Plain FIRST-LINE*'. The asterisk referred to the footnote 'NICE recommends MOVICOL Paediatric Plain first line for the treatment of constipation and faecal impaction in children'. Shire alleged that the advertisement did not clearly define the licensed indication for Movicol Paediatric Plain; the indication for a medicine, especially in children where there were important age restrictions, should be clear and unambiguous.

The advertisement did not state that NICE guidance recommended Movicol Paediatric for children younger than those it was licensed to treat. The NICE guidance in question cited doses of the paediatric formulation for use in children of under 1 year, 1-5 years and 5-12 years but stated in a footnote that '…Movicol Paediatric Plain… does not have UK marketing authorisation for use in faecal impaction in children under 5 years, or for chronic constipation in children under 2 years. Informed consent should be obtained and documented…'.

Shire noted that Movicol Paediatric Plain was indicated for the treatment of chronic constipation in children 2 to 11 years of age and for the treatment of faecal impaction in children from the age of five. Section 4.2 of the Movicol Paediatric Plain summary of product characteristics (SPC) stated 'Movicol Paediatric Plain is not recommended for children below five years of age for the treatment of faecal impaction, or in children below two years of age for the treatment of chronic constipation. For patients of 12 years and older it is recommended to use Movicol'

Shire alleged that claims that linked Movicol Paediatric Plain with the recommendation from NICE as '… first line for the treatment of constipation and faecal impaction in children' promoted treatment of those two conditions in children as young as 1 year old with this product. Shire noted that this was raised as a concern by the Panel in Case AUTH/2348/8/10. Shire had not seen the mailer at issue in that case, but understood from the case report that it included the footnote from the NICE guidance as noted above regarding the age of children for whom Movicol Paediatric Plain was licenced. The Panel, nonetheless, considered that the mailer potentially recommended the use of Movicol Paediatric Plain outside of its licensed indication. No such warning was included in the advertisement now at issue.

In summary, therefore, Shire alleged that the advertisement now at issue promoted use of Movicol Paediatric Plain outside of the terms of the marketing authorization. Shire further alleged that the claims were misleading, did not represent the NICE recommendation accurately or fairly, and did not encourage rational use of the medicine.

The Panel noted the comments from both parties regarding Case AUTH/2348/8/10. It noted that each case was considered on its own merits.

The Panel examined the advertisement now at issue. The copy included the claim and its asterisked footnote. The brand name Movicol Paediatric Plain and generic name were also included. The rest of the advertisement included a visual of a child holding a number 4 around which the words 'Bulk Soften Stimulate Lubricate' were

printed. The rest of the advertisement consisted of the prescribing information and the statement regarding reporting adverse events.

The only information about the patient population was given in the prescribing information which stated, in line with the SPC that Movicol Paediatric Plain was 'For the treatment of chronic constipation in children 2-11 years of age. For the treatment of faecal impaction in children from the age of 5 years'.

The Panel noted that the NICE guideline recommend the use of Movicol Paediatric Plain within the SPC indication. The NICE guideline also recommended use of the product outside the SPC. No mention of this was made in the advertisement. The advertisement might encourage health professionals to look at the NICE guideline. The Panel noted that the NICE guideline was clear regarding the licensed and unlicensed use of Movicol Paediatric Plain. This was a difficult situation. The NICE guideline recommended the use of Norgine's product and Norgine should be able to refer to this in its advertising whilst not advertising outside the licensed indication. The use of the product was given in the advertisement. If Norgine had mentioned the unlicensed NICE guideline recommendation in the advertisement then it could be argued that it was promoting outside the marketing authorization. Taking all the circumstances into account the Panel considered that the advertisement was not inconsistent with the Movicol Paediatric Plain SPC. The product had not been promoted outside its marketing authorization as alleged. No breach of the Code was ruled.

The Panel noted its comments above and did not consider that the claim was misleading as alleged; the NICE guideline had recommended Movicol Paediatric Plain for first line treatment. The advertisement was not such that it would not encourage rational use. No breaches of the Code were ruled.

Shire alleged that the promotion of a medicine outside of its marketing authorization, particularly for very young children, posed potentially serious patient safety concerns and was a failure to maintain high standards and brought the industry into disrepute.

The Panel did not consider that the advertisement promoted Movicol outside its marketing authorization. It thus did not consider that Norgine had failed to maintain a high standard. Nor had the company brought discredit to or reduced confidence in the pharmaceutical industry. No breaches of the Code including Clause 2 were ruled.

Shire had not seen the mailer at issue in Case AUTH/2348/8/10 and was not party to the undertaking given by Norgine in that case. As set out above it appeared from the case report that the claims at issue and ruling might also be relevant to the advertisement.

The Panel considered that the material at issue in Case AUTH/2348/8/10 was different to that now at issue. In the previous case the matters ruled upon were that the NICE guideline recommended the use of Movicol Paediatric Plain for children under 12 but had not referred to the adult formulation of Movicol. The Panel had queried whether Movicol Paediatric Plain had been promoted beyond the scope of its marketing authorization but there had been no complaint in that regard so the Panel had not made a ruling. There could be no breach of the undertaking given in Case AUTH/2348/8/10 and thus the Panel ruled no breach of the Code.

Shire noted that the leavepiece promoted Movicol for use in adults and children. One page included a similar stamp to that used in the advertisement at issue above. In the leavepiece the claim 'NICE Guideline recommends Movicol Paediatric Plain FIRST-LINE*' appeared as a stamp. The asterisk referred the reader to a second claim immediately below 'NICE Guideline CG99 recommends Movicol Paediatric Plain as the first-line treatment for constipation in children.'

Shire stated that its serious concerns about the advertisement were brought to Norgine's attention in late November 2010. In its response, Norgine agreed to suspend use of the advertisement pending conclusion of inter-company dialogue via a meeting. Shire understood this to include suspension of other promotional activities using this imagery, statements and claims. Shire and Norgine met in March 2011 to discuss issues raised by the advertisement. The leavepiece was offered at a UK gastroenterology annual meeting in March 2011 and used the same imagery and claims; it was prepared in January 2011 ie a month *after* Norgine agreed to suspend use of the advertisement pending inter-company dialogue. Due to the serious nature of the concerns raised over this campaign, Shire believed continued use of this campaign, including preparation of new items using the same claims and messages, constituted a failure to maintain high standards and brought the industry into disrepute.

The leavepiece lacked any warnings of the age restrictions for Movicol Paediatric Plain in comparison to the broader NICE guidance, and therefore also promoted this product outside of its marketing authorization. This marketing campaign for Movicol Paediatric Plain, in the form of the advertisement and the leavepiece had been used for at least nine months.

During this time prescribers could be left with a lasting impression that Movicol Paediatric Plain should be used first-line in children from one year old, as endorsed by NICE. Nowhere in the campaign did Norgine clearly advise prescribers of the lower age restrictions of this product (2 years for chronic constipation and 5 years for faecal impaction). Neither did the materials note the recommendation to obtain informed consent (as set out by NICE) when prescribing this agent to

children younger than in whom it was licensed. Shire considered that Norgine should issue a corrective and statement in the form of a 'Dear Doctor' letter to make these restrictions clear.

The Panel noted the accounts of inter-company dialogue in relation to the advertisement. Norgine had stopped using the advertisement until that matter had been settled. The Panel understood Shire's frustration about the use of the leavepiece which had been prepared after Norgine had suspended use of the advertisement. However the Constitution and Procedure did not require Norgine to suspend use of the advertisement at issue, nor the leavepiece in question. Failure to do so did not amount to a breach of the Code. Thus the Panel ruled no breaches of the Code including Clause 2.

Shire Pharmaceuticals Limited complained about the promotion of Movicol Paediatric Plain (polyethylene glycol (macrogol) 3350 plus electrolytes) by Norgine Pharmaceuticals Limited. At issue were an advertisement (ref MO/10/2014) which had appeared in Paediatric Nursing, November 2010 and a leavepiece (ref MO/2277/JAN/11).

That part of the complaint which involved an alleged breach of undertaking was taken up by the Director as the Authority was responsible for ensuring compliance with undertakings.

A Advertisement

1 Stamp 'NICE recommends MOVICOL Paediatric Plain FIRST-LINE*'

COMPLAINT

Shire noted the prominent 'stamp' image on the advertisement which stated 'NICE [National Institute for Health and Clinical Excellence] recommends MOVICOL Paediatric Plain FIRST-LINE' and submitted that Norgine had confirmed that it had used this endorsement without the written permission of NICE. Shire alleged a breach of Clause 9.6.

RESPONSE

Norgine confirmed that it had not sought permission from NICE to refer to its guidance in promotion as it did not consider that such permission was needed.

Clause 9.6 prohibited the reproduction of official documents in promotional material unless written permission had been given by the appropriate body. Reference to the NICE guideline in the advertisement did not constitute the reproduction of an official document and so Norgine did not believe that failure to seek permission to use was in breach of Clause 9.6.

PANEL RULING

The Panel did not consider that the use of a statement in promotional material that NICE had recommended a particular treatment meant that an official document had been reproduced as prohibited by Clause 9.6. The clause prohibited, for example, the reproduction of a prescription form without permission. The Panel did not consider that the claim at issue constituted reproduction of an official document as meant by Clause 9.6. The Panel ruled no breach of Clause 9.6.

2 Stamp 'NICE recommends MOVICOL Paediatric Plain FIRST-LINE*'

COMPLAINT

Shire stated that the specifics of which NICE guidance was referred to in the advertisement was not clear since it was not referenced anywhere. Norgine had confirmed that the document referred to was CG99 'Constipation in children and young people: Diagnosis and management of idiopathic childhood constipation in primary and secondary care'.

A breach of Clauses 7.6 and 7.8 was alleged.

RESPONSE

Norgine stated that Clause 7.6 stated that when promotional material referred to published studies, references must be given. NICE guidance was not a published study, it was a guideline issued by an official body which was easily accessible to all without the need for an exact reference. Norgine therefore submitted that just referring to a national guideline did not come under the scope of 'published studies' and hence there was no breach of Clause 7.6. It was possible, of course, to substantiate the statements by consulting the NICE guidance itself.

Clause 7.8 was quite specific in its scope, which was limited to the reproduction of artwork. No reproduction of artwork was involved in the advertisement; therefore there could be no breach of Clause 7.8.

PANEL RULING

The Panel noted that Clause 7.6 required a reference to be given when promotional material referred to published studies. The claim at issue did not refer to a published study. It would have been helpful to include a reference for the NICE guideline but failure to do so did not amount to a breach of Clause 7.6. Thus the Panel ruled no breach of that clause. The Panel noted that Clause 7.8 was similar but related to artwork, illustrations and graphs. The claim at issue was not from a published study and thus no breach of Clause 7.8 was ruled.

3 Stamp 'NICE recommends MOVICOL Paediatric Plain FIRST-LINE*'

The asterisk referred to the footnote 'NICE recommends MOVICOL Paediatric Plain first line for the treatment of constipation and faecal impaction in children'

COMPLAINT

Shire alleged that the advertisement did not clearly define the licensed indication for Movicol Paediatric Plain. Shire considered that the indication for a medicine, especially in children where there were important age restrictions, should be made clear and unambiguous.

The advertisement did not state that NICE guidance recommended Movicol Paediatric for children younger than those it was licensed to treat.

The NICE guidance in question (CG99) gave the doses of the paediatric formulation for use in disimpaction, and ongoing maintenance (chronic constipation, prevention of faecal impaction) for children of under 1 year, 1-5 years and 5-12 years but stated in a footnote:

> 'At the time of publication (May 2010) Movicol Paediatric Plain is the only macrogol licensed for children under 12 years that includes electrolytes. **It does not have UK marketing authorisation for use in faecal impaction in children under 5 years, or for chronic constipation in children under 2 years. Informed consent should be obtained and documented.** Movicol Paediatric Plain is the only macrogol licensed for children under 12 years that is also unflavoured.' (emphasis added).

Shire stated that Movicol Paediatric Plain was indicated:

> 'For the treatment of **chronic constipation** in children **2 to 11 years of age**. For the treatment of **faecal impaction** in children from the **age of five years**, defined as refractory constipation with faecal loading of the rectum and/or colon' (emphasis added).

Section 4.2 of the Movicol Paediatric Plain summary of product characteristics (SPC) also stated:

> 'MOVICOL Paediatric Plain **is not recommended for children below five years of age for the treatment of faecal impaction, or in children below two years of age for the treatment of chronic constipation**. For patients of 12 years and older it is recommended to use MOVICOL' (emphasis added).

Shire alleged that claims that plainly and directly linked Movicol Paediatric Plain with the recommendation from NICE as '… first line for the treatment of constipation and faecal impaction in children' promoted treatment of those two conditions in children as young as 1 year old with this product.

Shire noted that this point had been raised as a concern by the Panel in Case AUTH/2348/8/10. Shire had not seen the mailer (MO/10/1995) at issue in that case, but understood from the case report that it included a footnote that stated:

> '[MOVICOL Paediatric Plain] does not have a UK marketing authorisation for use in faecal impaction in children under 5 years and for chronic constipation in children under 2 years. Informed consent should be obtained and documented.'

The Panel, nonetheless, considered that the mailer potentially recommended the use of Movicol Paediatric Plain outside of its licensed indication. No such warning was included in the advertisement now at issue.

In summary, therefore, Shire alleged that the advertisement promoted use of Movicol Paediatric Plain outside of the terms of the marketing authorization in breach of Clause 3.2.

Shire further alleged that the claims were misleading, did not fairly or accurately represent the NICE recommendation and did not encourage rational use of the medicine, in breach of Clauses 7.2 and 7.10.

RESPONSE

Norgine denied that the advertisement recommended off-licence use. There was no specific content in the body of the advertisement which promoted use outside licence. The focus of the advertisement was to notify prescribers that Movicol Paediatric Plain was now recommended for first line use.

The advertisement contained prescribing information which was quite clear as to the licensed uses for the product. As with all prescribing information, prescribers were further directed to refer to the SPC before prescribing. The Movicol Paediatric Plain SPC made clear the ages of children for whom it was licensed. Therefore there was sufficient information in the advertisement to make it clear what the licensed age groups were for this product.

All NICE guidance documents stated the following on their first page: 'This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. **However, the guidance does *not* override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering'** (emphasis added).

Therefore it was clear that NICE guidelines did not have primacy when it came to a health professional prescribing a medicine for a patient. NICE guidance did not override the responsibility of health professionals to make prescribing decisions informed by the relevant SPC.

Norgine asserted that both the journal advertisement and the leavepiece (point B below) appropriately and sufficiently drew prescribers' attention to the fact that the guideline on treating constipation in children recommended Movicol Paediatric Plain as first-line treatment. Norgine submitted that it was reasonable to draw prescribers' attention to this fact, but it was up to them to make a prescribing decision only after referring to the SPC.

Norgine believed this was analogous to and consistent with the presentation of data that was derived from a clinical study containing off-licence data in promotional material. So long as the presentation of data within the context of the promotional item was within the product licence, it was acceptable to present the data which was within licence. Norgine therefore denied a breach of Clause 3.2.

Regarding the alleged breach of Clause 7.2, Shire had stated that the claims did not accurately reflect the NICE guidance and were thus misleading. However, Norgine was unable to identify exactly what Shire believed was misleading as it had not stated this clearly. The only interpretation Norgine could infer was that Shire believed it was misleading for Norgine not to have stated the age range considered by NICE, which according to the Panel's ruling in Case AUTH/2348/8/10 would be inappropriate. Regardless, Norgine did not believe it was misleading to refer only to a subset of the guidance, so long as the subset was representative of the overall guidance. There was no doubt, as the Panel had confirmed in Case AUTH/2348/8/10, that the guidance recommended Movicol Paediatric Plain for an age range that included that stated in the advertisement.

Shire had further alleged a breach of Clause 7.10 but had not indicated the basis for that allegation. The advertisement was clearly within the scope of the licence and the context of the NICE guidance. Therefore Norgine could not see what aspect was in breach of Clause 7.10.

PANEL RULING

The Panel noted the comments from both parties regarding Case AUTH/2348/8/10. It noted that each case was considered on its own particular merits.

The Panel examined the advertisement now at issue. The copy included the claim and its asterisked footnote. The brand name Movicol Paediatric Plain and generic name were also included. The rest of the advertisement included a visual of a child holding a number 4 around which the words 'Bulk Soften Stimulate Lubricate' were printed. The rest of the advertisement consisted of the prescribing information and the statement regarding reporting adverse events.

The only information about the patient population was given in the prescribing information which stated under the subheading 'uses' that Movicol Paediatric Plain was 'For the treatment of chronic constipation in children 2-11 years of age. For the treatment of faecal impaction in children from the age of 5 years'. This was in line with the SPC.

The Panel noted that the NICE guideline recommend the use of Movicol Paediatric Plain within the SPC indication. The NICE guideline also recommended use of the product outside the SPC. No mention of this was made in the advertisement at issue. The advertisement might encourage health professionals to look at the NICE guideline. The Panel noted that the NICE guideline was clear regarding the licensed and unlicensed use of Movicol Paediatric Plain. The Panel considered that this was a difficult situation. The NICE guideline recommended the use of Norgine's product and Norgine should be able to refer to this in its advertising whilst not advertising outside the licensed indication. The use of the product was given in the advertisement. If Norgine had mentioned the unlicensed NICE guideline recommendation in the advertisement then it could be argued that it was promoting outside the marketing authorization. Taking all the circumstances into account the Panel considered that the advertisement was not inconsistent with the Movicol Paediatric Plain SPC. The product had not been promoted outside its marketing authorization as alleged. No breach of Clause 3.2 was ruled.

The Panel noted its comments above and did not consider that the claim was misleading as alleged; the NICE guideline had recommended Movicol Paediatric Plain for first line treatment. The advertisement was not such that it would not encourage rational use. No breach of Clauses 7.2 and 7.10 were ruled.

4 Alleged breaches of Clauses 2 and 9.1

COMPLAINT

Shire alleged that there were potential serious patient safety concerns associated with the promotion of a medicine outside of its marketing authorization, particularly for very young children. Shire believed this constituted a failure to maintain high standards and brought the industry into disrepute.

RESPONSE

As stated above, Norgine did not consider the material was in breach of Clause 3.2 and so it could not see any grounds for concern in respect of

patient safety and therefore denied breaches of Clauses 2 and 9.1.

Given that NICE would never recommend an action that would place patient safety at risk and that the licensed indication for the product was clearly stated and that the presentation of the data in the advertisement had been constructed in response to the Panel's comments in Case AUTH/2348/8/10, it was difficult to see where high standards had not been maintained or safety placed at risk. Norgine therefore strongly denied any breach of Clause 9.1.

Whilst Norgine did not consider that the data was presented in such a way as to be considered promotional in children under the age of 2, Norgine's ongoing safety surveillance had not raised concerns which would cause it to challenge the position of NICE or the British National Formulary for Children.

Given that breaches of Clause 2 were reserved as a particularly serious censure, Norgine further denied the alleged breach of Clause 2.

Norgine made additional comments on the alleged breach of Clauses 2 and 9.1 at point B below.

PANEL RULING

The Panel noted its rulings in point A3. It agreed with the complainant that promoting a medicine outside its marketing authorization was a serious matter that could potentially have patient safety concerns. However the Panel did not consider that the advertisement promoted Movicol outside its marketing authorization. It thus did not consider that Norgine had failed to maintain a high standard. Nor had the company brought discredit to or reduced confidence in the pharmaceutical industry. No breach of Clauses 9.1 and 2 was ruled.

5 Alleged breach of undertaking

COMPLAINT

Shire had not seen the mailer (ref MO/10/1995) at issue in Case AUTH/2348/8/10 and was not party to the undertaking given by Norgine in that case. As set out in point A3 above it appeared from the case report that the claims at issue and ruling might also be relevant to the advertisement. Shire requested, therefore, that the Panel consider a breach of Clause 25.

RESPONSE

Norgine denied that it had breached its undertaking since that undertaking referred specifically and solely to the promotion of Movicol (the adult formulation) in the over 12s, not Movicol Paediatric Plain. Norgine therefore did not consider that this was a valid allegation, no undertaking in respect of promotion of Movicol Paediatric Plain was made and therefore no breach should be ruled.

PANEL RULING

The Panel considered that the material at issue in Case AUTH/2348/8/10 was different to that now at issue. In the previous case the matters ruled upon were that the NICE guideline recommended the use of Movicol Paediatric Plain for children under 12 but had not referred to the adult formulation of Movicol. The Panel had queried whether Movicol Paediatric Plain had been promoted beyond the scope of its marketing authorization but there had been no complaint in that regard so the Panel had not made a ruling. There could be no breach of the undertaking given in Case AUTH/2348/8/10 and thus the Panel ruled no breach of Clause 25.

B Leavepiece

The leavepiece promoted Movicol for use in adults and children. One page included a similar stamp to that used in the advertisement at issue above. In the leavepiece the claim 'NICE Guideline recommends Movicol Paediatric Plain FIRST-LINE*' appeared as a stamp. The asterisk referred to a second claim immediately below 'NICE Guideline CG99 recommends Movicol Paediatric Plain as the first-line treatment for constipation in children.'

COMPLAINT

Shire stated that its serious concerns about the advertisement were brought to Norgine's attention on 26 November 2010. In its response of 9 December 2010, Norgine agreed to suspend use of the advertisement pending conclusion of inter-company dialogue via a meeting. Shire understood this to include suspension of other promotional activities using this imagery, statements and claims. Shire and Norgine met on 18 March 2011 to discuss the issues raised by Shire about the advertisement.

The leavepiece was offered at the British Society of Gastroenterology's (BSG) annual meeting on 15 March 2011. It used the same imagery and claims. The date of preparation, January 2011, was one month *after* Norgine agreed to suspend use of the advertisement pending inter-company dialogue.

Due to the serious nature of the concerns raised over this campaign, Shire believed its continued use, including preparation of new items using the same claims and messages, constituted a failure to maintain high standards and brought the industry into disrepute. A breach of Clauses 2 and 9.1 was alleged.

The leavepiece lacked any warnings of the age restrictions for Movicol Paediatric Plain in comparison to the broader NICE guidance, and therefore also promoted the product outside of its marketing authorization, in breach of Clause 3.2. Shire stated that for at least nine months during which this marketing campaign, in the form of the advertisement and the leavepiece, had been used, prescribers could be left with a lasting impression

that Movicol Paediatric Plain should be used to treat chronic constipation or faecal impaction first-line in children from one year old, as endorsed by NICE. Nowhere in the campaign were prescribers advised of the lower age restrictions of this product (2 years for chronic constipation and 5 years for faecal impaction). Neither was the recommendation to obtain informed consent (as set out in the NICE guidance itself) when prescribing this agent to children younger than in whom it was licensed, mentioned.

Shire believed that the responsible course of action was for Norgine to issue a corrective and explanatory statement in the form of a 'Dear Doctor' letter to make these restrictions clear.

RESPONSE

Norgine was unclear as to Shire's specific concerns in respect of a breach of Clause 3.2 and assumed that the allegation had arisen because Norgine did not specify the difference between the licensed indication for Movicol Paediatric Plain and the age range stated in the NICE guideline. Since the leavepiece was in line with the licence and the undertaking in Case AUTH/2348/8/10, Norgine denied a breach of Clause 3.2.

Shire appeared to allege the breaches of Clause 2 and 9.1 on its assertion that Norgine ignored commitments made during inter-company dialogue. Norgine submitted that its letter of 9 December clearly demonstrated that this was not so.

The inter-company dialogue was protracted for various reasons however, in the spirit of the initial concerns raised by Shire, Norgine voluntarily offered to suspend the use of the journal advertisement whilst inter-company dialogue was on-going. This was a gesture of goodwill to enable the discussions to progress in a constructive manner and despite the protracted timeline in meeting, the advertisement remained suspended.

Neither in Shire's response to Norgine's letter of 9 December or at any other point prior to the meeting in March, did Shire request that Norgine suspend anything other than the advertisement.

Shire alleged that the continued use of the material constituted a failure to maintain high standards. There was no requirement in the Authority's Constitution and Procedure for a company to cease use of material in response to competitor concerns until such time as inter-company agreement had been reached.

Norgine took a responsible approach to reviewing material alleged to be in breach by competitors, and if it considered allegations to be founded, it took immediate action. However, Norgine did not consider other materials to be in breach of the Code on this occasion; hence the need for dialogue to better understand Shire's position. Norgine therefore denied the allegation of a breach of Clause 9.1. Norgine also denied the allegation of a breach of Clause 2, which was a particular censure reserved for the most serious matters.

Shire did not allege any specific breach relating to the length of time taken to hold the inter-company meeting. However, Norgine believed that there was an implied criticism but it strongly repudiated any suggestion that it was responsible for the delay. Norgine had hoped to have the inter-company meeting in early January ie as soon as possible after its proposal for such a meeting was agreed by Shire on 22 December. However, for various reasons the earliest mutually agreeable date for a meeting was 18 March. Norgine was very disappointed with the time it took to arrange this meeting, as it genuinely wanted to meet Shire as early as possible to explore its concerns about the material and see if a course of action could be agreed which might avoid any further complaints.

In relation to both the leavepiece and advertisement, Norgine stated that if the Panel ruled no breaches of some or all of the allegations Clauses 3.2, 7.2, 7.6, 7.8, 7.10, 9.6 and 25 there might be no case for a breach of Clause 9.1.

As Norgine did not consider the material to be in breach of Clause 3.2 it could not see any grounds for concern in respect of patient safety and it therefore denied breaches of Clause 9.1.

Given that NICE would never recommend an action that would place patient safety at risk and that the licensed indication for the product was clearly stated and that the presentation of the data in the advertisement had been constructed in response to the Panel's comments in Case AUTH/2348/8/10, it was difficult to see where high standards had not been maintained. Norgine therefore denied the allegation of a breach of Clause 9.1.

In relation to the alleged breach of Clause 2 on the leavepiece and advertisement, if the Panel ruled no breaches of some or all of the allegations, Clauses 3.2, 7.2, 7.6, 7.8, 7.10, 9.1, 9.6 and 25, there might be no case for a breach of Clause 2.

Norgine noted that Clause 2 was a sign of particular censure and should be reserved for such circumstances. Such circumstances would include, *inter alia*, prejudicing patient safety. Shire alleged that there were serious safety concerns associated with the promotion of Movicol Paediatric Plain outside of its marketing authorization.

The Panel needed to consider whether serious safety concerns existed in this specific case if it ruled a breach of Clause 3.2. Norgine contended that there were no serious safety concerns in respect of this product and that even if the Panel considered that the medicine had been promoted outside of its marketing authorization (an allegation which Norgine strongly refuted), then it was not the case that simply because the promotion was said to have been to very young children, that this made

any safety concerns raised automatically serious. Indeed, not only NICE but also the British National Formulary for Children recommended the use of Movicol Paediatric Plain in children under 2 years of age. Neither of these highly respected organisations would ever recommend anything that was even remotely likely to prejudice patient safety.

Norgine did not believe Shire had raised any other allegations in respect of the promotion of Movicol Paediatric Plain which might lead the Panel to consider that there had been a breach of Clause 2. Shire had, nonetheless, contended that Norgine's alleged breach of undertaking should give rise to a ruling of a breach of Clause 2. As stated in point A5 above, Norgine contended that there was no breach of undertaking. There was therefore no case to answer in this regard.

PANEL RULING

The Panel noted the accounts of inter-company dialogue in relation to the advertisement. Norgine had ceased use of the advertisement until that matter had been settled. The Panel understood Shire's frustration about the use of the leavepiece which had been prepared after Norgine had suspended use of the advertisement at issue in point A above.

However the Constitution and Procedure did not require Norgine to suspend use of the advertisement at issue, nor the leavepiece in question. Failure to do so did not amount to a breach of the Code. Thus the Panel ruled no breach of Clauses 9.1 and 2 of the Code.

Complaint received **11 April 2011**

Case completed **1 July 2011**

CASE AUTH/2399/4/11

RENAL ANAEMIA NURSE PRACTITIONER v VIFOR PHARMA

Promotion of Ferinject

A renal anaemia nurse practitioner alleged that an email relating to Ferinject (iron solution for injection/infusion), a Vifor Pharma product, was biased.

The complainant noted that the email suggested that use of Ferinject would deliver savings. It was not clear from the article within the email that other IV irons were available. The email referred to redesigning intravenous iron services, and encouraged the reader to view a video on Ferinject.

A detailed response from Vifor Pharma is given below.

The Panel noted that the complaint was only about the email which the complainant appeared to have received from a third party media company. Vifor had paid the media company a nominal fee to put the video, originally developed for use with NHS Alliance, onto its website. Given this relationship between the parties, the Panel considered that when the media company had distributed the video it had done so with Vifor's authority; Vifor was thus responsible under the Code for the media company's actions in that regard. The email, alerting recipients to the availability of the video, (as received by the complainant) stated that 'Currently, the treatment of iron deficiency involves multiple visits to the hospital but a drug called Ferinject from Vifor Pharma administers all the iron a patient needs in one 30 minute visit'. The Panel considered that this claim implied that Ferinject was the only iron replacement therapy that could be administered as a single total dose infusion and that all other products needed multiple visits, which was not so. The Panel thus considered that the claim was misleading and a breach of the Code was ruled.

A renal anaemia nurse practitioner complained about an email relating to Ferinject (iron solution for injection/infusion), a Vifor Pharma UK Limited product.

COMPLAINT

The complainant noted that the email suggested that use of Ferinject would deliver savings. It was not clear from the article within the email that other intravenous (IV) irons were available; as a non medical prescriber, the complainant considered it was biased.

The email stated:

> 'Redesigning intravenous iron services is an excellent way of delivering QIPP improvements to patient care by dramatically reducing hospital visits and improving service efficiency and cost-effectiveness.
>
> Currently, the treatment of iron deficiency involves multiple visits to the hospital but a drug called Ferinject from Vifor Pharma administers all the iron a patient needs in one 30 minute visit.
>
> Watch this video to find out how this patient-centric service is saving the NHS money and promoting faster recovery and better outcomes.'

When writing to Vifor Pharma, the Authority asked it to respond in relation to Clause 7.2 of the Code of Practice.

RESPONSE

Vifor Pharma explained that it was asked by NHS Alliance, organisers of the November 2010 Alliance Annual Conference, to contribute to 'NHS Alliance TV News', an hour long video, which was to be shown at the meeting and used on the NHS Alliance website. The conference theme was to focus on the Quality, Innovation, Productivity and Prevention (QIPP) Initiative and in that regard the NHS Alliance suggested that redesigning iron services would be an appropriate example to highlight the benefits of QIPP initiatives. The topics were agreed and a contract signed with the story title of 'Delivering QIPP by redesigning iron services'.

Vifor noted that the QIPP Initiative was driven at a national, regional and local level to support clinical teams and NHS organisations to improve the quality of care they delivered while making efficiency savings that could be reinvested in the service to deliver year on year quality improvements.

Vifor stated that currently, up to five visits were needed to administer 1g of its medicine Venofer (200mg/visit). Most patients who received this treatment had co-morbid conditions including chronic kidney disease, end stage renal disease and other chronic conditions. The video highlighted the fact that by using an alternative preparation, Ferinject, these patients could be given 1g in one 30 minute visit with resultant benefits consistent with the QIPP program.

Vifor provided speakers for the video and allowed filming at its premises. The script was reviewed internally for the general manager. The video was signed off according to Vifor's internal procedures.

Vifor stated that, in response to a request to do so, it allowed a media company to host the video on its

website. The article and video belonged to the NHS Alliance and Vifor did not proactively contact anyone to disseminate either. The media company emailed only those registered users of its website who had previously signed up to receive emails regarding new information on the website.

The complainant did not receive the email from Vifor, it was sent by the media company.

When, on 26 April 2011, Vifor realised that the media company was not affiliated to the NHS Alliance it asked for the immediate removal of the video.

While Vifor now appreciated that some might consider the video to be promotional, it was produced specifically as a non-promotional, independent endorsement of QIPP, to highlight an example of how a patient centric service supported the QIPP Initiative. Vifor thus did not consider that the complaint's concerns were valid.

In response to a request for further information Vifor reiterated that the NHS Alliance approached it to give an example of IV iron services supporting QIPP and after internal discussions Vifor decided to participate in the project.

Following the NHS Alliance Conference, videos used during the conference were hosted on the NHS Alliance website. When the media company asked Vifor if it could put the NHS Alliance QIPP video on its website, Vifor understood that organisation to be part of the NHS Alliance initiative. There was a nominal fee to host the video. Vifor had two days' notice to agree, and unfortunately gave its consent without checking the affiliation to NHS Alliance. As soon as Vifor realised that the media company was an independent organisation outside the NHS Alliance it asked that the video be removed and it was removed immediately.

The video was signed off internally specifically for the NHS Alliance project.

PANEL RULING

The Panel noted that the complaint was only about the email which the complainant appeared to have received from the media company. Vifor had paid the media company a nominal fee to put the video, originally developed for use with NHS Alliance, onto its website. Given this relationship between the parties, the Panel considered that when the media company had distributed the video it had done so with Vifor's authority; Vifor was thus responsible under the Code for the media company's actions in that regard. The email, alerting recipients to the availability of the video, stated that 'Currently, the treatment of iron deficiency involves multiple visits to the hospital but a drug called Ferinject from Vifor Pharma administers all the iron a patient needs in one 30 minute visit'. The Panel considered that this claim implied that Ferinject was the only iron replacement therapy that could be administered as a single total dose infusion and that all other products needed multiple visits, which was not so. At least one other medicine (Cosmofer, marketed by Vitaline) could be administered in this way albeit over 4-6 hours. The Panel thus considered that the claim was misleading as alleged. A breach of Clause 7.2 was ruled.

During its consideration of this case, the Panel noted that the video, produced for use by the NHS Alliance, had been filmed at Vifor's offices, Vifor had provided speakers and had reviewed the script for the general manager. The video had been certified under the Code. The Panel was concerned to note, however, that Vifor considered that the video was non-promotional. In the Panel's view the video clearly promoted Ferinject and to consider otherwise demonstrated a very poor understanding of the Code and its requirements. The Panel questioned whether, as promotional material, the video complied with the Code and noted that, at the very least, it should have contained the prescribing information for Ferinject. In the Panel's view, Vifor would be well advised to review the video and its status under the Code and it requested that the company be advised of its extreme concerns in this regard.

Complaint received	**13 April 2011**
Case completed	**27 June 2011**

CASE AUTH/2400/4/11

NOVO NORDISK v BAXTER

Promotion of FEIBA

Novo Nordisk complained about the promotion of FEIBA (Factor VIII Inhibitor Bypassing Activity) by Baxter. The materials at issue were a double-sided single page document 'Introducing the FEIBA Prophylaxis Algorithm' and a six page brochure 'FEIBA A systematic treatment approach' which featured the claim 'Up to 85% reduction in bleed frequency'.

Novo Nordisk queried whether the claim reflected the available evidence as some reports suggested that the response rate to FEIBA was highly variable (range 50-90%). Novo Nordisk considered that the 'Up to 85%...' claim demonstrated cherry picking of favourable data and was therefore misleading.

The detailed response from Baxter is given below.

The Panel noted that the claim was referenced to Perry *et al* (2010) which summarized paediatric and adult data on FEIBA prophylaxis. The results given for reduction in bleed frequency varied from 57-85% for children and 50-90% for adults. Perry *et al* summarized the position that in patients with severe haemophilia and inhibitors, FEIBA prophylaxis had been shown to reduce the frequency of bleeding by up to 85% and to improve patient quality of life.

The Panel considered that the selection of 85% for the claim up to 'Up to 85% reduction in bleed frequency' was misleading as it did not reflect all the evidence contemporaneous with when it was used. A breach of the Code was ruled.

Novo Nordisk Limited complained about the promotion of FEIBA (Factor VIII Inhibitor Bypassing Activity) by Baxter Healthcare Ltd. Inter-company dialogue had failed to resolve all of Novo Nordisk's concerns.

The materials at issue were a double-sided single page document, 'Introducing the FEIBA Prophylaxis Algorithm (ref ADV 09/2758B) and a six page brochure 'FEIBA A systematic treatment approach' (ref ADV 09/2815B).

The claim at issue 'Up to 85% reduction in bleed frequency' was referenced to Perry *et al* (2010). Novo Nordisk stated that on closer inspection of Table 2, the reference attributed to this claim (reference 31 within Perry *et al*) originated from an abstract by Valentino (2008) which was presented as a poster at the World Federation of Haemophilia congress in 2006.

COMPLAINT

Novo Nordisk queried whether the claim reflected all the available evidence clearly, as reports from other published evidence (as seen in Tables 2 and 3 of Perry *et al*) suggested that the response rate to FEIBA was highly variable (range 50-90%). Novo Nordisk believed that the use of this efficacy figure in a promotional context ('Up to 85% bleed reduction') demonstrated cherry picking of favourable data at one end of a highly variable results range. Novo Nordisk alleged that the claim was misleading as it did not reflect the evidence clearly in breach of Clause 7.2 of the Code.

Novo Nordisk noted that the abstract by Valentino reported on a single patient with haemophilia B and inhibitors. FEIBA was licensed for use in haemophilia A patients with an inhibitor and was not licensed for use in patients with haemophilia B. Furthermore, it was well documented that there was a potential and significant risk of anaphylaxis with the use of FEIBA in patients with haemophilia B and specific mutations.

In inter-company dialogue Baxter had stated that, in response to a request for advice from the Authority, about the use of a reference that included a haemophilia B inhibitor patient to support a claim around use in a haemophilia A inhibitor patient, the Authority had advised that 'it was acceptable to use such an article as substantiation for a promotional claim however such an article could not be used promotionally by the sales force'.

Novo Nordisk was not convinced that Baxter had followed the Authority's advice, as it was aware that a Baxter representative had handed over a copy of Perry *et al* within a reprint folder (ref ADV09/2711B) at the UK Haemophilia Centre Doctors' Organisation (UKHCDO) meeting in Newcastle in November 2010.

RESPONSE

Baxter stated that in its view Perry *et al* fully substantiated the claim, and it rejected the allegation that it was using a haemophilia B patient case as the source of the figure quoted.

This article was the result of a meeting of an expert panel of clinicians, all of whom had experience in this use of FEIBA from their clinical practice. The purpose of the meeting was to review all the published evidence in this area and then devise evidence-based guidance on how FEIBA should be used to best effect. The results of this review of the evidence was clearly stated in the publication abstract and summary; the authors concluded

'regular FEIBA prophylaxis has been shown to reduce the frequency of bleeding by up to 85%'. This was the source of the number Baxter quoted in its claim.

This publication included data relating to 86 children and 32 adults, all with haemophilia A and inhibitors, therefore all in the patient group where FEIBA was licensed.

It was coincidental that the single case reported by Valentino in this article referred to exactly the number quoted in the claim. Excluding possible double-counting of haemophilia B cases less than 2% of the total cohort fell into that category; as at least 95% of the cases reported were within the licence for FEIBA Baxter did not accept the allegation.

Baxter was not surprised that this case report was highlighted as it was the only one in Perry *et al* to refer to cost of treatment, and Baxter had been in dispute with Novo Nordisk for some time over cost-effectiveness claims it made for its product NovoSeven compared with FEIBA.

In addition, Baxter would only use a conference abstract to substantiate an efficacy claim where no other published evidence existed. This was clearly not the case; however it seemed that Novo Nordisk was not prepared to accept this, however Baxter made the point, or however often it stated it.

Baxter did not claim 'FEIBA prophylaxis reduces bleed frequency by 85%' – although this specific figure was stated in the reference, such an absolute statement would be factually inaccurate.

Baxter noted that the other publication by Valentino cited in Perry *et al*, a retrospective case series reporting experience with six patients, suggested that an 84% reduction in bleeding episodes was in fact the mean percentage reduction, and not the upper limit.

Baxter submitted that response to treatment in this patient group could indeed be variable, whichever product was used. That said, there was an equal variation in the dose and frequency of treatment between case series. Despite this, the authors stated that the results of case series 'consistently demonstrate the efficacy and safety of FEIBA prophylaxis'. The individual case studies presented by the authors to illustrate their individual experience reinforced this.

What was also clear from the Perry article was that in many situations the use of FEIBA to prevent bleeding achieved exactly that outcome – the incidence of bleeding in these patients had become comparable to that seen in haemophilia patients without inhibitors, and in some cases no bleeding episodes were seen while on treatment.

Baxter maintained that the claim at issue was accurate and substantiated by the reference; it fairly reflected the evidence available. Baxter rejected the allegation of a breach of Clause 7.2. In a subsequent letter Baxter stated that the claim at issue had been withdrawn due to recently published data that materially affected it.

PANEL RULING

The Panel noted that after it had submitted its response, Baxter withdrew the claim pending revision due to new evidence. The new evidence was not identified. The Panel decided that in the circumstances it would consider the complaint in relation to its use prior to withdrawal.

The Panel noted that the claim was referenced to Perry *et al* (2010) which summarised paediatric and adult data on FEIBA prophylaxis. The results given for reduction in bleed frequency varied from 57-85% for children (Table 2 of Perry *et al*) and 50-90% for adults (in two of the studies in Table 3 of Perry *et al* the mean reduction in bleed frequency was 53% with a range of 10-85%). Perry *et al* summarised the position that in patients with severe haemophilia and inhibitors, FEIBA prophylaxis had been shown to reduce the frequency of bleeding by up to 85% and to improve patient quality of life.

The Panel considered that the selection of 85% for the claim up to 'Up to 85% reduction in bleed frequency' was misleading as it did not reflect all the evidence contemporaneous with when it was used. A breach of Clause 7.2 was ruled.

Complaint received	**15 April 2011**
Case completed	**7 June 2011**

CASE AUTH/2402/4/11

JOURNALIST v BAYER

Tweets about Levitra and Sativex

A reporter with a healthcare publication provided a copy of an article from InPharm entitled 'Digital Pharma: Bayer UK's Twitter slip-up' which discussed two tweets posted by Bayer Healthcare about Levitra (vardenafil) and Sativex (delta-9-tetrahydrocannabinol and cannabidiol) and the Code.

The InPharm article stated that the tweets at issue were notable compared with other UK pharma twitter accounts which signed their tweets off by medical and legal departments and were confined to disease awareness or healthcare news from the mainstream press. The author noted that some of the approximately 500 Bayer twitter account followers were clearly members of the public. The article referred to the PMCPA guidance on the use of digital media.

The complainant raised a number of questions regarding the use of twitter and the Code.

The detailed response from Bayer is given below.

The Panel noted that the Code prohibited the advertising of prescription only medicines to the public. Information could be supplied directly or indirectly to the public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific prescription only medicine.

The Panel noted that social media, including twitter, could be used to provide information to the public so long as the material complied with the Code. In its guidance on digital communications (issued April 2011) and in relation to twitter, the Authority had stated that 'If a company wanted to promote a medicine via twitter it would have to ensure that if the medicine was prescription only, the audience was restricted to health professionals and that the message, in addition to any link to further information, complied with the Code. In addition companies would also have to ensure that recipients had agreed to receive the information. Given these restrictions and the character limit on twitter, it is highly unlikely that the use of this medium to promote prescription only medicines would meet the requirements of the Code'.

The Panel noted that the tweets at issue were taken from the headlines of certified press releases and were posted on the same days as the respective news releases. The tweets themselves were not certified. The twitter account was accessible by members of the public.

The Levitra tweet did not cite the product's name but referred to its qualities, indication and launch. The Sativex tweet mentioned the brand name, indication and launch. The Panel considered that each tweet was in fact a public announcement about the launch of a prescription only medicine which promoted that medicine to the public and would encourage members of the public to ask their health professionals to prescribe it. Breaches of the Code were ruled in relation to each tweet as acknowledged by Bayer. The Panel considered that high standards had not been maintained. A further breach of the Code was ruled.

The Panel was concerned that material placed on twitter had not been certified. That the original press releases were certified was insufficient in this regard. If part of a certified document was reproduced in a different format or directed to a different audience the new material should be certified separately. The Panel was extremely concerned that controls within the company were such that uncertified information about the launch of prescription only medicines had been posted on twitter. A breach of Clause 2 was ruled.

A reporter with a healthcare publication provided a copy of an article from InPharm entitled 'Digital Pharma: Bayer UK's Twitter slip-up' which discussed tweets posted by Bayer Healthcare about Levitra (vardenafil) and Sativex (delta-9-tetrahydrocannabinol and cannabidiol) and the Code.

The article was subtitled 'There seems to be some confusion at Bayer UK over what communications can be sent over Twitter' and referred to two tweets: the first announced the launch of a new formulation of Levitra 'First & only melt-in-the-mouth erectile dysfunction treatment launched by Bayer today http://tinyurl.com/6hfxymf' and the second read 'Savitex launched in UK for the treatment of spasticity due to Multiple Sclerosis http://tiny.cc.kiz2y'. The tweets were posted on 22 March 2011 and 21 June 2010 respectively. The InPharm article stated that the tweets at issue were notable compared with other UK pharma twitter accounts which signed their tweets off by medical and legal departments and confined themselves to disease awareness or healthcare news from the mainstream press. The article noted that some of the approximately 500 Bayer twitter account followers were clearly members of the public and referred to the PMCPA guidance on the use of digital media.

COMPLAINT

The complainant questioned whether the Authority considered that the tweets breached the Code and whether it would take action. The complainant also asked how concerned the PMCPA was about the use of twitter and social media to promote pharmaceutical products and whether there was a need for a separate Code giving guidance about acceptable use of social media given the popularity of twitter, facebook etc.

When writing to Bayer Healthcare, the Authority asked it to respond in relation to Clauses 2, 9.1, 22.1 and 22.2 of the Code.

RESPONSE

Bayer stated that the two product-specific tweets in question for Levitra and Sativex were posted on 22 March 2011 and 21 June 2010 respectively. The tweets were taken from the headlines of certified news releases and were posted on the same days as the respective news releases. The tweets themselves were not certified.

Bayer's UK/Ireland twitter channel currently had approximately 550 'followers' the majority of whom had a special interest in Bayer's businesses: journalists, agencies, consultants and other service providers, students, competitors and other Bayer contacts. However, given that the provision of 'follower' details was discretionary, it was not possible to identify exactly who they represented. A list of 'followers' was provided.

On re-examining the tweets after receiving the complaint from the PMCPA and, in particular, in the context of the Panel's rulings in Case AUTH/2355/9/10 about a news story on a company website, Bayer accepted that the tweets constituted advertising to the public and an encouragement to request a specific medicine and therefore were in breach of Clauses 22.1 and 22.2.

As made clear in the Digital Communications Guidance, issued by the PMCPA, April 2011, it was an ongoing challenge for the pharmaceutical industry to decide how it could use digital media and still ensure it respected the long established restrictions on promoting its products. This complaint had greatly assisted Bayer to establish what use could be made of digital media by its pharmaceutical business. Together with the rest of the industry, Bayer was keen to continue to work with the PMCPA to ensure that it did its very best to use the constantly developing opportunities of new media to support high quality patient care within the boundaries established by the Code.

In accepting breaches of Clauses 22.1 and 22.2, for which Bayer extended its sincere apologies to the PMCPA, Bayer referred to the rulings in Case AUTH/2355/9/10 in the hope that its tweets were not such as to require the Panel to rule a breach of either Clauses 9.1 or 2.

PANEL RULING

The Panel noted that Clause 22.1 prohibited the advertising of prescription only medicines to the public. Clause 22.2 permitted information to be supplied directly or indirectly to the public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific prescription only medicine.

The Panel noted that the use of social media including twitter to provide information to the public was a legitimate activity so long as the material complied with the Code, particularly Clause 22.

In its guidance on digital communications (issued April 2011) and in relation to twitter, the Authority had stated that 'If a company wanted to promote a medicine via twitter it would have to ensure that if the medicine was prescription only, the audience was restricted to health professionals and that the message, in addition to any link to further information, complied with the Code. In addition companies would also have to ensure that recipients had agreed to receive the information. Given these restrictions and the character limit on twitter, it is highly unlikely that the use of this medium to promote prescription only medicines would meet the requirements of the Code'.

The Panel noted that the tweets were taken from the headlines of certified press releases and were posted on the same days as the respective news releases. The tweets themselves were not certified. The twitter account was accessible by members of the public.

The Levitra tweet did not cite the product's name but referred to its qualities, indication and launch. According to the article provided by the complainant the tweet was linked to the press release. Bayer had not commented on this. The Sativex tweet mentioned the brand name, indication and launch. The Panel considered that each tweet was in fact a public announcement about the launch of a prescription only medicine. The Panel considered that each tweet promoted a prescription only medicine to the public and would encourage members of the public to ask their health professionals to prescribe it. Breaches of Clauses 22.1 and 22.2 were ruled in relation to each tweet as acknowledged by Bayer. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel considered that the circumstances of the present case were different to Case AUTH/2355/9/10 cited by Bayer wherein no breach of Clause 2 was ruled in relation to the short description of a press release on the open access homepage of

company website and the press release itself. Breaches of Clauses 9.1, 22.1 and 22.2 had been ruled. Case AUTH/2355/9/10 thus concerned material published in a different format. There was no allegation or comment in that case as to whether the material at issue had been certified. Turning to the present case, the Panel was concerned that material placed on twitter had not been certified. That the original press releases were certified was insufficient in this regard. If part of a certified document was reproduced in a different format or directed to a different audience the new material should be certified separately.

The Panel was extremely concerned that controls within the company were such that uncertified information about the launch of prescription only medicines had been posted on twitter. The nature of dialogue on twitter was such that tweets were broadly and quickly disseminated. A breach of Clause 2 was ruled.

Complaint received **28 April 2011**

Case completed **3 June 2011**

MEDA v ALK-ABELLÓ

Promotion of Jext

Meda complained about a leavepiece issued by ALK-Abelló for its adrenaline auto-injector Jext which was indicated for the emergency treatment of severe acute allergic reactions as well as idiopathic or exercise induced anaphylaxis.

Meda alleged that two diagrams, entitled 'Jext is designed to be easy to use', failed to accurately reflect the instructions for use in the marketing authorization of the product and exaggerated the simplicity of use of the device. The diagrams were derived from the product labelling but were not accompanied by explanatory text. Meda submitted that this was an incomplete depiction of the use of the product.

Meda considered that adrenaline auto-injectors were a technical and emotive treatment and their correct use depended on accurate information and comprehensive training. The Jext device was used differently from the current market leader and ALK-Abelló was obliged to present the instructions for use clearly and explicitly.

Whilst Meda did not dispute the claim that Jext was 'designed to be easy to use' it questioned whether the administration of adrenaline in an anaphylactic emergency was ever simple and submitted that it was untrue that Jext was simpler than other adrenaline auto-injector devices.

The detailed response from ALK-Abelló is given below.

The Panel compared the steps illustrated in the leavepiece with those included in Section 6.6 of the Jext summary of product characteristics (SPC). There were five illustrated steps in the SPC and two in the leavepiece. The two diagrams in the leavepiece were identical to the two diagrams on the barrel of the auto-injector itself. The only patient instruction included in the SPC which was not illustrated on the leavepiece was the final step to massage the injection area for 10 seconds and seek urgent medical help. The explanatory text next to the diagrams in the SPC noted that the black tip of auto-injector must be placed against the outer thigh and the auto-injector held at a 90º angle to the thigh. The Panel considered that these two requirements were clear in the two diagrams that appeared in the leavepiece.

The Panel considered that although only two of the five SPC diagrams had been reproduced in the leavepiece, the leavepiece did not exaggerate the simplicity of using Jext as alleged. The Panel further considered that Jext had been promoted in accordance with the terms of its marketing authorization; it did not consider that the claim 'Jext is designed to be easy to use' implied that administration of adrenaline was simple or that Jext was simpler to administer than other auto-injector devices as alleged. No breach of the Code was ruled on all the three points.

Meda Pharmaceuticals Limited complained about a leavepiece (ref 600AD) issued by ALK-Abelló Limited for its adrenaline auto-injector Jext. Jext was indicated for the emergency treatment of severe acute allergic reactions (anaphylaxis) to insect stings, foods, drugs and other allergens as well as idiopathic or exercise induced anaphylaxis. Meda also supplied an adrenaline auto-injector (EpiPen) for allergic emergencies.

COMPLAINT

Meda alleged that two small diagrams on the inside front flap of the leavepiece, entitled 'Jext is designed to be easy to use', failed to accurately reflect the instructions for use in the marketing authorization of the product, in breach of Clause 3.2 of the Code, and exaggerated the simplicity of use of the device, in breach of Clause 7.2.

The two diagrams were derived from the product labelling but were not accompanied by explanatory text. Meda submitted that this was an incomplete depiction of the use of the product. To put this into context, Meda noted that the summary of product characteristics (SPC) for Jext listed five steps for administration.

Meda noted that on the facing page of the leavepiece, the Jext device was shown unboxed, which, during inter-company dialogue, ALK-Abelló had stated was an adequate representation to the reader for complete instruction. Meda disagreed and submitted that even if the device was pictured on the same page, the reader would not be given a clear indication of the full instructions for use.

Adrenaline auto-injectors were a technical and emotive treatment and their correct use depended on accurate information and comprehensive training. The Jext device was used differently from the current market leader and ALK-Abelló was obliged to present the instructions for use clearly and explicitly.

Whilst Meda did not dispute the claim that Jext was 'designed to be easy to use' it questioned whether the administration of adrenaline in an anaphylactic emergency was ever simple and submitted that it

was untrue that Jext was simpler than other adrenaline auto-injector devices.

RESPONSE

ALK-Abelló stated that the promotional leavepiece was designed to be used with health professionals who were experienced prescribers of adrenaline auto-injectors. The leavepiece was not part of the patient training support programme for Jext; separate materials were available for this purpose.

ALK-Abelló submitted that the two diagrams on the inside front flap reproduced in full the illustrations used on the Jext auto-injector integral instructions for use, as approved by the Medicines and Healthcare products Regulatory Agency (MHRA) and 14 other European agencies. The leavepiece was designed so that at all times the recipient could clearly view two actual size photographs of Jext 300mcg and Jext 150mcg showing the instructions for use as displayed on the approved labelling.

ALK-Abelló stated that the illustrated, integral instructions for use were one of the enhanced safety features designed into Jext based on 15 years of feedback about adrenaline auto-injectors from health professionals, patients and carers. The leavepiece was designed to highlight these features to experienced adrenaline auto-injector prescribers as they would know that many patients failed to use their device correctly in the event of a potentially life-threatening anaphylactic reaction.

ALK-Abelló submitted that it was a commonly held belief that cartridge based adrenaline auto-injectors (such as Jext and EpiPen) had a two step activation process and that syringe based adrenaline auto-injectors (such as Anapen) had an extra operational step. Diagrams showing the two main steps of the activation process for cartridge based devices were included on both the US and UK EpiPen websites, included in Meda's EpiPen leavepiece and EpiPen instructions for use, and approved by the MHRA for inclusion on the device label for Jext, as illustrated in the leavepiece at issue.

ALK-Abelló submitted that the two actual size photographs of the approved, built-in instructions for use included on the leavepiece enabled the recipient to form their own opinion as to the simplicity or otherwise of Jext. The leavepiece was sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine, and all information provided was in accordance with the terms of the Jext marketing authorization and consistent with the Jext SPC.

ALK-Abelló denied breaches of Clauses 3.2 and 7.2 of the Code.

PANEL RULING

The Panel noted that the therapeutic indication for Jext listed in the SPC for the product was the emergency treatment of severe acute allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise induced anaphylaxis.

The Panel noted ALK-Abelló's submission that the leavepiece was for use with health professionals who were experienced prescribers of adrenaline auto-injectors. The leavepiece was not for use with patients. ALK-Abelló had submitted that separate patient training materials were available.

The Panel compared the steps illustrated in the leavepiece with those included in Section 6.6 of the Jext SPC. There were five illustrated steps in the SPC and two in the leavepiece. The two diagrams in the leavepiece were identical to the two diagrams on the barrel of the auto-injector itself. The only patient instruction included in the SPC which was not illustrated on the leavepiece was the final step to massage the injection area for 10 seconds and seek urgent medical help. The explanatory text next to the diagrams in the SPC noted that the black tip of auto-injector must be placed against the outer thigh and the auto-injector held at a 90° angle to the thigh. The Panel considered that these two requirements were clear in the two diagrams that appeared in the leavepiece.

The Panel considered that although only two of the five SPC diagrams had been reproduced in the leavepiece, the leavepiece did not exaggerate the simplicity of using Jext as alleged. No breach of Clause 7.2 was ruled. The Panel further considered that Jext had been promoted in accordance with the terms of its marketing authorization. No breach of Clause 3.2 was ruled.

The Panel did not consider that the claim 'Jext is designed to be easy to use' implied that administration of adrenaline was simple or that Jext was simpler to administer than other auto-injector devices as alleged. No breach of Clause 7.2 was ruled.

Complaint received **27 May 2011**

Case completed **5 July 2011**

CASE AUTH/2408/6/11

HOSPITAL CONSULTANT v ABBOTT LABORATORIES

Provision of conference bags

A non-contactable consultant rheumatologist, complained about the provision of a conference bag with Abbott's name on it at the European League Against Rheumatism (EULAR) meeting in London, held between 25-28 May 2011. The complainant was puzzled by the provision of the bag given the requirements of the 2011 Code and that the grace period for complying with the new requirements had passed.

The detailed response from Abbott is given below.

The Panel noted that the Code requirements relating to promotional aids had recently changed. Under the 2008 Code, promotional aids were permitted, whether related to a particular product or of general utility, to be distributed to members of the health professions and to appropriate administrative staff, provided that the promotional aids were inexpensive and relevant to the practice of the recipient's profession or employment. The 2011 Code defined a promotional aid as a 'non-monetary gift made for a promotional purpose' and prohibited the provision of promotional aids to health professionals and appropriate administrative staff, with the exception of inexpensive notebooks, pens and pencils for use when attending scientific meetings and conferences, promotional meetings and other such meetings.

The Panel noted that the sponsorship of the conference bags was by the Abbott international team based in France, rather than Abbott UK, and that this sponsorship was not notified to Abbott UK. It was an established principle under the Code that UK companies were responsible for the acts and omissions of their overseas affiliates that came within the scope of the Code. The EULAR meeting was held in the UK and thus covered by the UK Code.

The Panel noted that the Abbott international team notified the EULAR organisers about its choice of sponsorship package on 15 September 2010. The Panel noted that the 2011 Code became effective on 1 January 2011, with a transition period until 30 April 2011 to comply with newly introduced provisions. The Panel noted that the EULAR meeting in question took place on 25-28 May 2011, after the end of this transition period. The provision of a conference bag as a promotional aid at the time of the EULAR meeting was no longer acceptable. A breach of the Code was ruled.

A non-contactable consultant rheumatologist, complained about the provision of a conference bag with Abbott's name on it at the European League Against Rheumatism (EULAR) meeting in London, held between 25-28 May 2011.

The front flap of the bag had the EULAR meeting logo and dates on the right hand side and 'Abbott' on the left hand side, with 'A Promise for Life' immediately below the company's name.

COMPLAINT

The complainant stated that, given the requirements of the 2011 Code and that the grace period for complying with the new requirements had passed, he was puzzled by the provision of a conference bag with Abbott's name on it. When this was raised with a company official the complainant was told that international conferences were exempt from the Code. This did not make sense to the complainant and when he asked another official from Abbott he was informed that since the bags were bought before the deadline period of 1 May 2011, they were not covered by the 2011 Code. The complainant considered that if that was so, he would continue to see representatives distributing gifts even after 10 years because all would use the excuse that the gifts were either booked or purchased before the cut-off period. The complainant stated that receiving two different answers from two different officials raised his suspicions and so he asked a third person – this time a senior official of Abbott, who to the complainant's amazement provided a third story! According to that person, when Abbott paid organisers its sponsorship money, it was not sure of its intended use and were very concerned that the organisers had decided to spend it towards bags!! Three different versions within three days! The complainant provided a copy of the official booklet produced by the EULAR organisers which listed various advertising options. Conference bags were listed as promotional materials at €55,000 plus VAT. The complainant was unhappy and now realised that the senior official of Abbott was not speaking the truth about Abbott not knowing the intended use of its sponsorship money. Apparently, it knew when it booked these promotional bags that its money would be used towards conference bags and also knew that the meeting would be held after the end of the grace period given in the Code.

When writing to Abbott Laboratories Limited, the Authority asked it to respond in relation to Clause 18.1 of the Code.

RESPONSE

Abbott submitted that as the annual EULAR congress was an international meeting, the

planning and execution of the company's activities was led by its international colleagues. In doing so, the international colleagues in France were aware that, as well as the EFPIA Code and the regulations set out by the congress organisers, the regulations of the host country must be adhered to.

As EULAR 2011 was hosted in London, members of the Abbott UK medical department liaised closely with international Abbott colleagues in order to communicate the relevant requirements of the Code and to certify activities and materials. Nearly 60 such items were certified in the UK.

As part of Abbott's activities at EULAR 2011, the international Abbott team decided to become a corporate sponsor of the congress. Integral to that sponsorship was the opportunity to link the company's corporate logo to a particular item or service that all delegates would receive as part of their registration package. Abbott elected to include the Abbott logo on the official EULAR 2011 congress bag. The Abbott international team confirmed this decision in an email sent to the EULAR 2011 conference organisers on 15 September 2010. This activity was seen by Abbott international as corporate sponsorship. Unfortunately, the international team did not appreciate that corporate sponsorship activities fell within the scope of the Code and therefore this sponsorship arrangement was not notified to Abbott UK. Given this, Abbott UK could not review this activity in relation to compliance with the Code and as such did not certify the material as required under Clause 14 of the Code. This was clearly a failing of internal communication and a point that the company would ensure was addressed in all future relevant activities.

The conference bags were distributed at an official EULAR desk located within the EULAR registration area. Registered delegates arriving at the conference were initially directed to the first official EULAR desk at which they received their congress badge. They then moved on to a second official EULAR desk at which they were given a series of items on behalf of EULAR, including, but not limited to, the official congress bag in question, the EULAR abstract book, an Oyster card, the password for wireless internet access and the final programme.

Other than bearing the corporate Abbott logo, there was no link between Abbott and provision of the bag to delegates.

PANEL RULING

The Panel noted that the Code requirements relating to promotional aids had recently changed. Under the 2008 Code, Clause 18.2 permitted promotional aids, whether related to a particular product or of general utility, to be distributed to members of the health professions and to appropriate administrative staff, provided that the promotional aids were inexpensive and relevant to the practice of the recipient's profession or employment. Under new provisions in the 2011 Code, Clause 1.7 defined a promotional aid as a 'non-monetary gift made for a promotional purpose' and Clause 18.1 prohibited the provision of promotional aids to health professionals and appropriate administrative staff, subject to Clauses 18.2 and 18.3. Clause 18.3 permitted the provision of inexpensive notebooks, pens and pencils for use when attending scientific meetings and conferences, promotional meetings and other such meetings.

The Panel noted that the sponsorship of the conference bags was by the Abbott international team based in France, rather than Abbott UK, and that this sponsorship was not notified to Abbott UK. It was an established principle under the Code that UK companies were responsible for the acts and omissions of their overseas affiliates that came within the scope of the Code. The EULAR meeting was held in the UK and thus covered by the UK Code.

The Panel noted that the Abbott international team notified the EULAR organisers about its choice of sponsorship package on 15 September 2010. The Panel noted that the 2011 Code was agreed by ABPI members on 2 November 2010 and became effective on 1 January 2011, with a transition period until 30 April 2011 to comply with newly introduced provisions. Prior to agreement there had been much discussion about the proposed changes to the Code and of course the consultation requirements in the Constitution and Procedure had been met. The Panel noted that the EULAR meeting in question took place on 25-28 May 2011, after the end of the transition period. The provision of a conference bag as a promotional aid at the time of the EULAR meeting was no longer acceptable.

The Panel appreciated that agreement to sponsor international events such as the EULAR meeting often took place well in advance of the meeting being held. However, Abbott UK submitted that it had liaised closely with international Abbott colleagues in order to communicate the relevant requirements of the Code and to certify activities and materials. The Panel noted the explanation that the Abbott international team considered sponsorship to be a corporate activity and considered that the arrangements should have ensured that all activity taking place at the UK conference was captured. The Panel considered that the sponsorship of the conference bag was unacceptable and a breach of Clause 18.1 of the 2011 Code was ruled.

Complaint received **14 June 2011**

Case completed **6 July 2011**

CODE OF PRACTICE REVIEW – August 2011

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

2378/12/10	**Primary Care Medical Director v Pfizer**	**Promotion of Champix**	**Breaches Clauses 7.2 and 7.9**	**Appeal by respondent**	**Page 3**
2380/1/11	Merz v Allergan	Promotion of Botox and alleged breach of undertaking	No breach	No appeal	Page 11
2382/1/11	General Practitioner v Novo Nordisk	Articles in Daily Mail	No breach	No appeal	Page 17
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2389/2/11	**Allergan v Alcon**	**Promotion of Travatan**	**Two breaches Clause 7.2** **Two breaches Clause 7.3** **Two breaches Clause 7.10** **Breach Clause 9.1**	**Appeal by respondent**	**Page 31**
2390/2/11	Anonymous representative v Alcon	Promotion of Azarga	No breach	No appeal	Page 45
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2393/3/11	**Voluntary admission by Baxter**	**Failure to take the ABPI Medical Representatives Examination within first year**	**Breach Clause 16.3**	**No appeal**	**Page 58**
2394/3/11 and 2395/3/11	**Boehringer Ingelheim v Lundbeck and Teva**	**Promotion of Azilect**	**Breaches Clauses 1.7 and 3.2** **Three breaches Clause 7.2** **Breaches Clauses 7.4 and 7.10** **Two breaches Clause 9.1** **Three breaches Clauses 22.2**	**Appeal by respondents**	**Page 61**
2397/3/11	Hospital Consultant v Warner Chilcott	Promotion of Asacol	No breach	Appeal by respondent	Page 71
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2400/4/11	**Novo Nordisk v Baxter**	**Promotion of FEIBA**	**Breach Clause 7.2**	**No appeal**	**Page 85**
2402/4/11	**Journalist v Bayer**	**Tweets about Levitra and Sativex**	**Breaches Clauses 2 and 9.1** **Two breaches Clause 22.1** **Two breaches Clause 22.2**	**No appeal**	**Page 87**
2405/5/11	Meda v ALK-Abelló	Promotion of Jext	No breach	No appeal	Page 90
2408/6/11	**Hospital Consultant v Abbott Laboratories**	**Provision of conference bags**	**Breach Clause 18.1**	**No appeal**	**Page 92**

PMCPA | 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, over 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 prescription only medicines made available to the 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, buy or sell 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 sponsorship of attendance at meetings organised by third parties
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio or video-recordings in any format, broadcast media, non-print media, the Internet, interactive data systems and the like.

It also covers:

- the provision of information on prescription only medicines to the public either directly or indirectly, including by means of internet
- relationships with patient organisations
- the use of consultants
- non-interventional studies of marketed medicines
- the provision of items for patients
- the provision of medical and educational goods and services
- grants and donations to institutions.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the four members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. One member of the Panel acts as case preparation manager for a particular case and that member is neither present nor participates when the Panel considers it.

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 William Harbage QC, and includes independent members from outside the industry. Independent members, including the Chairman, are always in a majority when matters are considered by the Appeal Board.

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 under the Code should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY

telephone 020 7747 8880
facsimile 020 7747 8881
by email to: complaints@pmcpa.org.uk.